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The suspended step of the stork

Editorial

Vassilios Barbounis

Over the past decades, major leaps were made in cancer treatment. We set off by administering (practically blindly) agents that promised some response and we are now able to provide targeted treatments for specific molecular paths. Clinical outcomes are improving; nevertheless, the hoped-for "healing" is not attained and research continues, as we try to understand exactly what happens in cancer cells –just like S. Faber and other pioneers in cancer research kept asking themselves.

The need for better management of the plethora of therapeutic information in order to improve outcomes with reduction in toxicity, led to the development of treatment guidelines for cancer patients. Production and implementation of guidelines is a whole chapter in cancer treatment, integrating the methodology and validation of summarized consensus statements, as well as the selection of patients and medical professionals that might use them; personal or collective liability; financial impact; legal standing; medical accountability, and, finally, assessment of the produced benefit or harm for the individual or the society. Unfortunately, guidelines cannot provide an answer to the anxious failing effort to save a patient that finally perishes.

The rules for using off-label drugs in order to protect patients from precarious treatments and retain costs are an even greater obstacle: administered only to a limited number of patients, for a particular disease-stage and specific dosage or route of administration, deprive patients with rare tumors from life-saving medicines. Pharmaceutical companies, as owners of the drugs, will not spend on sound approvals without return on investment, and conversely (due to the absurd bureaucracy and extensive legal procedures) research teams fail to embark on such an effort. The fight against cancer which started a few decades ago now continues at a different level, namely against chaotic red tape and administrative inflation. The cost increase in oncology research is disproportionate compared to the associated benefit obtained; and the State bears a great deal of responsibility for that.

In the current issue of FCO, S. Retsas [FCO 2013; 4(2):9-11], an experienced oncologist, comments -bitterly- on the discussion on the *Medical Innovation Bill* which is to be introduced in the British Legislature and the imminent changes on clinical trials legislation to be voted in the European Parliament. It remains to be proven whether the new legislation promotes cancer research or oncologists are in for a new race to save as many cancer patients as possible.

Cancer and the Law: Exhausting the resources of the art

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ABSTRACT

There is hardly an oncologist who has not stood frustrated at the bedside of a patient losing the battle with cancer. Options of licensed drugs available for other indications but not endorsed by license or in guidelines for a particular tumour, yet potentially valuable as a last resource, are instruments often denied to the physician and to that individual patient.

Exhausting the resources of the art, in these days of austerity and overregulated medicine, is a rare privilege of which most oncologists and their eager patients are deprived.

This paper discusses the introduction of the *Medical Innovation Bill* to the British Legislature which intends to address such crucial issues for cancer sufferers, as well as the new Proposals of the European Commission on clinical trials on medicinal products for human use and the withdrawal of Directive 2001/20/EC. Both are likely to have an impact on cancer care in Europe and beyond.

Key words: cancer; clinical trials; ethics; legislation; regulation; European Union.

…τῶν μὲν οὖν ἄλλων ἰατρῶν οὐδεὶς ἐθάρρει βοηθήσειν… Φίλιππος δ' ὁ Ἀκαρνὰν μοχθηρὰ μὲν ἑώρα τὰ περὶ αὐτὸν ὄντα, τῇ δὲ φιλίᾳ πιστεύων, καὶ δεινὸν ἡγούμενος εἰ κινδυνεύοντι μὴ συγκινδυνεύσει μέχρι τῆς ἐσχάτης πείρας βοηθῶν καὶ παραβαλλόμενος, ἐπεχείρησε φαρμακείᾳ καὶ συνέπεισεν αὐτὸν ὑπομεῖναι καὶ πιεῖν…

…none of the other physicians had the courage to administer remedies… but Philip the Acarnanian, who saw that the king was in an evil plight, put confidence in his friendship, and thinking it a shameful thing not to share his peril by exhausting the resources of the art in trying to help him even at great risk, prepared a medicine and persuaded him to drink it boldly… (Translation by Bernadotte Perrin) [1].

Plutarch's Lives: ALEXANDER XVIII. 3 - XIX. 2

There is hardly an oncologist who has not stood frustrated at the bedside of a patient losing the battle with cancer. Options of licensed drugs available for other indications but not endorsed by license or in guidelines for a particular tumour, yet potentially valuable as a last resource, are instruments often denied to the physician and to that individual patient.

Exhausting the resources of the art, in these days of austerity and overregulated medicine by the state or insurance companies, is a rare privilege of which most oncologists and their eager patients are deprived. Impregnable bureaucracy, excessively costly anti-cancer drugs, the spectrum of failure and perhaps even fear of one's ruined reputation, not unusually with the potential for litigation, confine many oncologists to passivity and inaction beyond the "standard treatment".

Better informed patients and their advocates are now mobilising support for breaking such barriers to therapy.

Following a family tragedy such an initiative was taken recently by Maurice Saatchi, an influential figure in the political scene of Britain.

At an innovations meeting hosted by the Royal Society of Medicine in London on 30th April 2013, Lord Saatchi presented for discussion

his proposed *Medical Innovation Bill*, with the provocative title *"How can an act of parliament cure cancer?"* [2-4].

He argued that the present pre-eminence in law of the *standard procedure*, outlaws initiative and provides no inducement to progress.

He further pointed out that the present state of the law exposes patients to *harmful inaction* as a result of the uncertainties of litigation, as well as to irresponsible innovation and leaves much doubt about what is best practice in innovation.

Present law makes the *status quo* -the "standard" treatment- the only safe option and gives clinicians no confidence in how to pursue responsible innovation. The author of the bill is eager to point out that innovation in cancer treatment does not necessarily imply greater expenditure; instead it is conceivable that innovation may involve the use of a drug or process already commonplace for other conditions, and which may well be less expensive than the standard treatment for that particular condition [4].

There are a number of unanswered questions before this new Bill is enacted; most crucially, how can one distinguish a responsible clinician eager to innovate from an irresponsible one who may cause harm.

Nevertheless, the Bill recognises and highlights problems only too familiar to oncologists in today's routine clinical practice and may potentially facilitate innovation at the bedside as effectively as innovation through the randomised mega-trials, if not more efficiently [5].

The debate on the *Medical Innovation Bill* in Britain coincides with new proposals by the European Commission on the regulation of clinical trials on medicinal products for human use, whilst repealing Directive 2001/20/EC [6].

There are approximately 4400 applications annually for clinical trials in the European Union (including the European Economic Area); 60% of these are sponsored by the pharmaceutical industry and the rest largely by Academia. Approximately 24% of all clinical trials applied for in the EU are multinational in purpose, i.e. trials intended to be performed in at least two Member States [6].

Although the implementation of Directive 2001/20/EC has arguably brought about significant improvements in the safety and ethical soundness of clinical trials, critics contend that it had also many direct effects on the cost and feasibility of conducting clinical trials which, in turn, have led to a decline in clinical trial activity in the EU. The number of applications for clinical trials dropped by 25% from 2007 to 2011, whereas insurance fees for industry sponsors have increased by 800%. The average delay for launching a clinical trial has increased by 90% to 152 days [6].

The stated intention of the new Clinical Trials Directive is to simplify the process for application and approval of trials through one portal and make it more uniform throughout the EU. It also includes a lighter regime for low-risk trials, for example, those using licensed medicines [6]. The latter echoes some aspects of the British *Medical Innovation Bill* [2-4].

In his discussion and analysis of the new European Directive, Peter C Gøtzsche, Director of the Nordic Cochrane Centre in Denmark highlighted some of its deficiencies in the fields of transparency and public access to information, consent, trial conduct, accountability and archiving. He warned that the drug industry has been lobbying the European Commission and members of the European parliament to prevent greater transparency about their trials and public access to all results and data; the latter being an issue that has been eagerly embraced by the British Medical Journal [7]. He urged action if the final form of this new Regulation is to be influenced in the interests and welfare of trial participants [8].

Joerg Haford, responding to Gøtzsche's paper, further contended that Brussels is driven essentially by competitive motives, intending to make Europe an advantageous location for trial sponsors by introducing in the new Directive a centralised approval process with extremely shortened timelines [9]. He also argued that in violation of international guidelines and ethical codes, a comprehensive and independent consideration and vote by a multidisciplinary Ethics Committee was no longer required in the draft new Directive, a view shared by others [9, 10].

It is reassuring to note that the Directive clearly states in Chapter V (Protection of subjects and informed consent, Article 28 General rules, page 45) that *"The rights, safety and well-being of the subjects shall prevail over the interests of science and society"* [6].

What is not stated however is as important! To this end, the ongoing debate has influenced some amendments to the original draft, especially on ethical issues. For example, amendment 7 (Proposal for a regulation Recital 14) now states *"Member States, when determining the appropriate body or bodies, should ensure the involvement of an* ***independent ethics committee*** *which includes healthcare professionals, lay persons and patients or patient representatives"* [11].

Currently, the ethics review procedure varies greatly between Member States. In order to bring clarity and consistency into the ethical review of clinical trials, without imposing the burden of full harmonisation, the Commission should set up a platform to encourage cooperation and the sharing of best practices between ethics committees. Participation in this platform should be voluntary but a State can demonstrate its concern for the welfare of its citizens through active participation [11].

On the issue of transparency, the amendment (added) states that, once a clinical trial has led to marketing authorisation, data generated during the clinical trial should be fully accessible and not considered commercially confidential [11].

The task for these and other amendments now rests on the lead rapporteur, Glenis Willmott MEP [12]. The Committee

vote was scheduled for the afternoon of Wednesday 29th May 2013. Assuming the report is adopted, the rapporteur will then enter negotiations with the European Council (Emily Hunter - Office of Glenis Willmott MEP personal communication 23/05/2013).

Oncologists and patients have no illusions that an act of Parliament -be it British, European or any other- can bring about the cure of cancer. It can, however, facilitate research both at the bench and the bedside, whilst ensuring the welfare and safety of participating patients.

In the meantime, every patient stricken with cancer hopes that once in their lifetime they will meet the Acarnanian Physician who will be ready to exhaust the resources of the art.

Note: This paper was presented in part at the *International Hippocratic Foundation of Kos* during the 4th Amphictyony, held under the Presidency of Professor Stephanos Geroulanos, 27-30 June 2013.

Conflict of interest statement

The author declares no conflict of interest.

REFERENCES

1. Retsas S. Alexander's (356-323 BC) expeditionary Medical Corps 334-323 BC. Journal of Medical Biography 2009; 17:165-169. DOI: 10.1258/jmb.2009.009001.
2. Saatchi M. How can an act of parliament cure cancer? J R Soc Med 2013; 106:169-172.
3. http://www.publications.parliament.uk/pa/bills/lbill/2012-2013/0061/en/20130061en.pdf (Last accessed 22-05-2013).
4. A guide to the Medical Innovation Bill as introduced in the House of Lords. London 10/04/2013. (Handout available to participants at an Innovations Meeting of the Royal Society of Medicine on 30th April 2013).
5. Retsas S. Treatment at Random: The Ultimate Science or the Betrayal of Hippocrates? JCO 2004; 22(24):5005-5008.
6. Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC. European Commission 2012. http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf. (Last Accessed 19-05-2012).
7. British Medical Journal Open Data Campaign. http://www.bmj.com/open-data (last visited 23/05/2013).
8. Gøtzsche PC. Deficiencies in proposed new EU regulation of clinical trials. BMJ 2012; 345:e8522.
9. Joerg Hasford. Deficiencies in proposed new EU regulation of clinical trials. BMJ 2012; 345:e8522. Rapid response 23 December 2012.
10. Toussaint B. EU Clinical Trials Regulation. Lancet 2013; 341:1719-1720.
11. http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//NONSGML+COMPARL+PE-504.236+01+DOC+PDF+V0//EN&language=EN (Last accessed 23/05/2013).
12. Willmott G. Draft European Parliament Legislative Resolution on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC (COM(2012)0369 - C7-0194/2012 - 2012/0192(COD)) (Ordinary legislative procedure: first reading) http://www.europarl.europa.eu/oeil/popups/ficheprocedure.do?reference=2012/0192(COD)&l=EN. Last accessed 23/05/2013).

Biologically effective dose-response relationship and the use of postoperative hypo-fractionated radiotherapy for early breast cancer patients treated by breast-conserving surgery

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ABSTRACT

Background: The purpose of the study was to find a biologically effective dose (BED)-response for postoperative breast radiotherapy (RT) for early-stage breast cancer, which would be useful in the clinical use of modified-hypofractionated radiotherapy schedules.

Patients & Methods: Tumour control probability (TCP) after RT was calculated based on data from existing randomised trials of adjuvant RT vs. non-RT. Using mainly the linear-quadratic formula, parameters such as the average initial number of clonogens per tumour before RT, and the average tumor cell radiosensitivity (alpha-value) were calculated. An α/β ratio of 4Gy was assumed for breast cancer cells.

Results: A linear regression equation was calculated: $-\ln[-\ln(TCP)] = -\ln(N_0) + \alpha^*BED = -4.08 + 0.07^*BED$, proposing a rather low radiosensitivity of breast cancer cells (alpha=0.07Gy^{-1}). A BED-response curve was constructed.

Conclusions: After a BED of about 90Gy$_4$ corresponding to a physical dose of 50-60Gy, TCP was shown to make a plateau. The proposed model could be an approximate guide in the use of non-standard dose fractionation (higher than 1.8-2Gy per fraction) and in the design and reporting of clinical trials of adjuvant breast RT.

Key words: adjuvant breast radiotherapy; fractionation; dose-response; hypofractionation.

INTRODUCTION

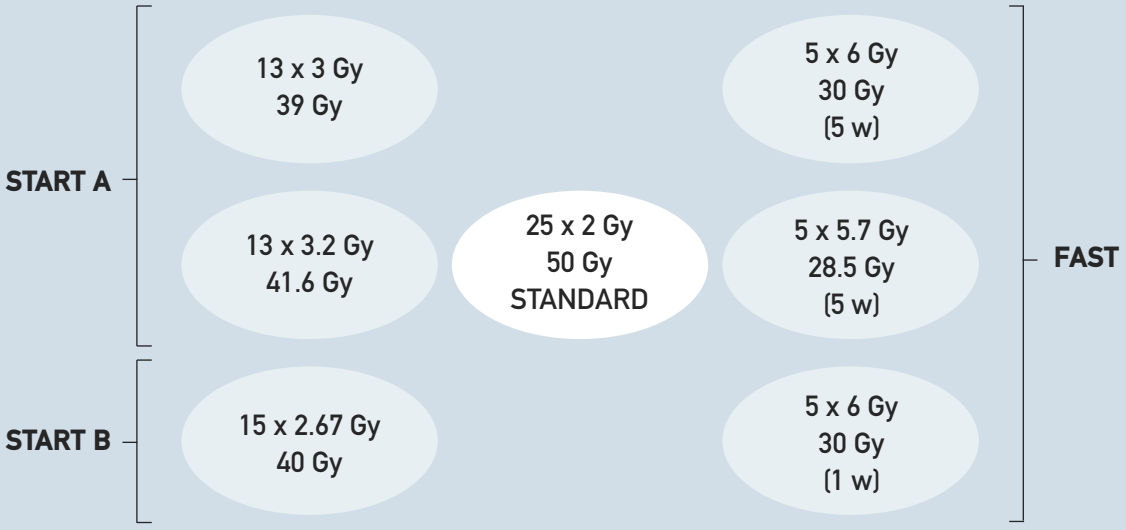
Although postoperative radiotherapy (RT) for early breast cancer treated by lumpectomy is an established treatment, the issue of optimal, for both patients and health providers (given the high numbers of breast cancer patients), RT dose and fractionation schedule remains unresolved. The most popular schedule for whole breast irradiation is 50Gy in 25 fractions over 5 weeks, while a variety of shorter (hypofractionated) RT schedules has also been used in clinical practice, mainly in the UK and Canada.

In a randomised controlled trial (RCT) from Canada, Whelan *et. al.* [1] have reported equivalent results (local control, survival and post-radiation effects) between the standard fractionation schedule of 50Gy in 25 fractions over 32 days and a hypofractionated scheme of 42.5Gy in 16 fractions over 22 days, for women with node-negative early breast cancer. Another short RT schedule (40Gy in 15 fractions) has been employed traditionally at the Christie Hospital in Manchester, with results comparable to those reported from other centres [2-4].

However, the most influential trials are the recently published START (Standardizing Radiotherapy) trials from the UK. START A trial [5] has shown that 41.6Gy/13 fractions or 39Gy/13 fractions are similar to the control regimen of 50Gy/25 fractions in terms of local-regional tumour control and late normal tissue effects, a result consistent with the result of START Trial B [6], which has shown that a radiation schedule of 40Gy/15 fractions offers equivalent results with the standard schedule of 50Gy/25 fractions (Figure 1).

Therefore, the need for establishing a dose-response relationship for postoperative breast radiotherapy is increasingly needed as a) modified fractionation is being broadly used [1-9]; b) there is an international interest for the accelerated partial breast radiotherapy,

Figure 1.
The modified-hypofractionated schedules compared with the standard of 50Gy in 25 fractions.



especially with IMRT [10, 11] and partial breast RT; and c) highly hypofractionated RT schedules are being explored currently, such as the FAST trial (FASTer Radiotherapy for breast cancer), which investigates the limits of hypofractionation for breast cancer RT i.e. five fractions of 5.7Gy or 6.0Gy delivered over 2-5 weeks [12, 13] (Figure 1).

In Greece, where radiotherapy resources are rather poor for a European country, hypofractionated RT schedules for postoperative breast RT could be of interest (with a meticulous treatment planning being needed, though), as RT slots would be spared and more patients would be accommodated. Moreover, people living in remote areas from radiotherapy facilities (e.g. islands) would find a shorter RT course more convenient [14, 15].

It has been anticipated that the fractionation sensitivity of breast cancer clonogens is rather high and similar to that of normal late reacting tissues and therefore, the value of α/β ratio of the LQ-model (Linear Quadratic) has been confirmed by START trials to be approximately 4Gy [5, 6, 16]. As a result, the size of dose per fraction in postoperative breast RT is expected to significantly influence the therapeutic results. Based on the principles of clinical radiobiology [17], the biologically effective dose (BED) reflects the relatively high fractionation sensitivity of breast tumours, a fact that would make the use of a BED-response relationship more clinically relevant than a simple dose-response one.

In the present study, we have attempted to find the underlying BED-response relationship with the use of existing data from RCT of postoperative vs. no postoperative RT in early breast cancer patients.

MATERIALS & METHODS

A thorough research of the literature for randomised controlled trials comparing lumpectomy alone vs. lumpectomy plus RT has shown nine published randomised trials demonstrating that breast irradiation substantially reduces the risk of local recurrence and prevents the need for subsequent mastectomy (Table 1).

Those studies have used dose/fractionation schedules ranging from 40Gy/15 fractions to 50Gy/25 fractions for the whole breast RT. The BED for each RT schedule was calculated by [17]:

$$BED = n \times d\,[1+d/(\alpha/\beta)]$$

Alpha/beta value for tumour control of breast cancer was taken as equal to 4Gy (see above) and repopulation was assumed to be small and not taken into account. An important issue is the calculation of the TCP from clinical data. As proposed by Withers *et al.* [27] TCP should be calculated as

$$TCP = \frac{\text{failure rate without RT - failure rate with XRT}}{\text{failure rate without XRT.}} \quad (1)$$

For example, if the recurrence rate was 5% in irradiated patients compared with 25% in surgery-only patients, the TCP (expressed as a percentage) is 25 – 5/25; that is, 80%, rather than 95%. The second from the right column in Table 1, contains the calculated TCPs from RCT. The surviving fraction (S) of cells after an RT regimen may be calculated from BED via the relationship:

$$BED = -\frac{\ln(S)}{\alpha} \Rightarrow S = e^{-a*BED}$$

If N_0 is the initial number of cells before RT (remaining after the preceding surgery, chemotherapy) then number (N), the number of cells surviving after RT, is:

$$N = N_0 \times S.$$

Given that a tumour is controlled when every single clonogenic cell has been eliminated then the tumour control probability (TCP) if we assume a Poisson distribution of the surviving cells is:

$$TCP = e^{-N} = e^{-N_0 S} = e^{-N_0 e^{-a*BED}}$$

Hence

$$\ln(TCP) = -N_0 e^{-a*BED} \Rightarrow \ln[-\ln(TCP)] = \ln(N_0) - a*BED \Rightarrow$$
$$\Rightarrow \ln[-\ln(TCP)] = -\ln(N_0) + a*BED \quad (2)$$

Hence plotting –ln[-ln(TCP)] (y-axis) against BED (x-axis) will give a straight line of slope α and intercept -ln(N_0), these parameters representing the averages over the considered population.

RESULTS

Simple linear regression performed with equation (2) above has given

$$-\ln[-\ln(TCP)] = -\ln(N_0) + \alpha*BED = -4.08 + 0.07*BED$$

This equation corresponds to the graph in Figure 2. Hence $\alpha=0.07Gy^{-1}$ and $N_0=59.15$. Therefore, the alpha coefficient of the LQ-model for breast cancer cells is estimated at $0.07Gy^{-1}$, indicating a rather radioresistant cell population [17]. This, however, is a common finding when cohorts are analysed and is usually ascribed to inter-tumour heterogeneity; in particular patients with the most radioresistant tumours (low α) have a marked influence in reducing the derived group average. This value certainly represents an average value ($\alpha_{effective}$) useful for some insight in the process. In addition, we have calculated that the average initial number

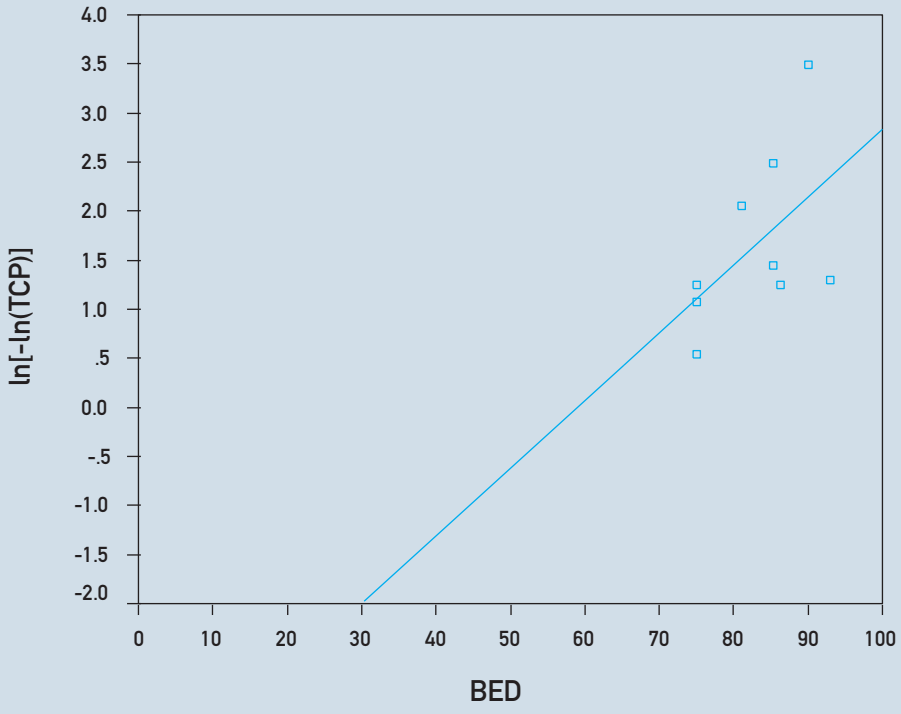
Table 1.

Studies of postoperative RT vs. no RT for breast cancer patients treated by breast preservation surgery. The last 4 studies are boost vs. no boost after whole breast RT. In the first two columns, each 1st row corresponds to the number of patients, and the 2nd to the % of local recurrence, followed by the follow-up length.

	No RT	RT	RT schedule	TCP*	BED (Gy_4)
Fisher *et al.*	570 27.9%	567 7.7% (5 y)	50Gy/25#	72	75
Liljegren G *et al.*	197 18.4%	184 2.3%	54Gy/27#	87.5	81
Malstrom *et al.*	587 14%	591 4%	48-54Gy/20-25#	71.4	75
Holli *et al.*	72 18%	80 8% (6.7 y)	50Gy/25#	55.5	75
					BED breastRT+boost
Clark *et al.*	421 25.7%	416 5.5% (4 y)	40Gy/16# + 12,5Gy/5#	78.6	65+20=85
Veronesi *et al.*	273 8.8%	294 0.3% (39 m)	50Gy/25# + 10Gy/5	96.6	75+15=90
Forrest *et al.*	294 24.5%	291 5.8% (5.7 y)	50Gy/20-25 + Boost 10-15 Gy OR Ir	76.3	75-81+15=90-96 (average 93)
Hughes *et al.*	319 4%	317 1%	45Gy/25# + 14Gy/7#	75	65+21=86
Fyles *et al.*	383 7.7%	386 0.6%	40Gy/16# + 12,5Gy/5#	92	65+20=85

(*) TCP was calculated as: TCP = (failure rate without RT – failure rate with RT) / failure rate without RT. (#): number of fractions

Figure 2.
Fitted linear regression line corresponding to the
-ln[-ln(TCP)] = -ln(No) + α * BED = -4.08 + 0.07* BED equation.



of clonogens per tumour (to be killed by adjuvant RT) is 59.15. Then, best-fit sigmoid relationship between TCP and BED can be reconstructed (Figure 3).

DISCUSSION

Difficulties in dose-response calculation

In the current study we used the method proposed by Withers *et al.* [27]: biological effectiveness of adjuvant irradiation should be measured by the percentile decrease in recurrence rate, rather than by improvements in the rate of control, so demonstration of success in clinical trials of adjuvant therapy is more likely the higher the recurrence rate in untreated controls (no RT patients groups). This should be taken into account when reporting and calculating TCPs in adjuvant treatments in oncology. However, the difficulty in establishing such a dose-response relationship in postoperative breast RT may be relatively greater than for some other solid tumours, given that:

a) an unknown percentage of patients actually have no residual cancer cells left following operation, while others have a subclinical (microscopic) amount of residual tumour cells that must be eradicated by radiation [27, 28]. This is an inherent problem when analysing the results of any adjuvant therapy;

b) dose-escalation studies are usually lacking, therefore any information should be obtained only from randomised controlled trials (RCT) of RT vs. no RT where a narrow range of RT schedules has been used; and

c) biological aggressiveness (ranging from elderly patients with T1N0, grade 1 hormone-receptor positive tumours to women with multiple positive nodes, hormone receptor negative, HER2 positive tumours), variable surgical techniques and skills amongst centres, chemotherapy/endocrine regimes and timing and radiotherapy techniques are some of the factors that may seriously affect the homogeneity of clinical data in the randomised trials examined. In addition, local recurrence could be the result of tumour regrowth of within the initial tumour bed; or of tumour in the same breast but outside the initial tumour bed, arising from cells existing there at the time of initial treatment; or, finally, a *de novo* development of a new tumour in the same breast. This source of heterogeneity also contributes to an overall decrease in the slope of the response curve.

Therefore, given the heterogeneity of the clinical material, the calculated α–value in this and similar studies is rather a measure of an *-effective* value. Although an effective alpha (α) of 0.07Gy^{-1} is seemingly characteristic of a low radiosensitivity cell population, an assumed homogeneous

radiosensitivity coefficient, (although not biologically sound) is workable for the interpretation of clinical data, as has been reported elsewhere [29].

We have also found that the pre-RT average clonogen number per tumour is 59. This low value is also, in part, a consequence of the "flattened out" population response curve. A further reason for a low N_0 value is that the residual hierarchical status of differentiating tumours will cause them to have quite small numbers of relatively undifferentiated regenerative cells [30].

The optimal fractionation

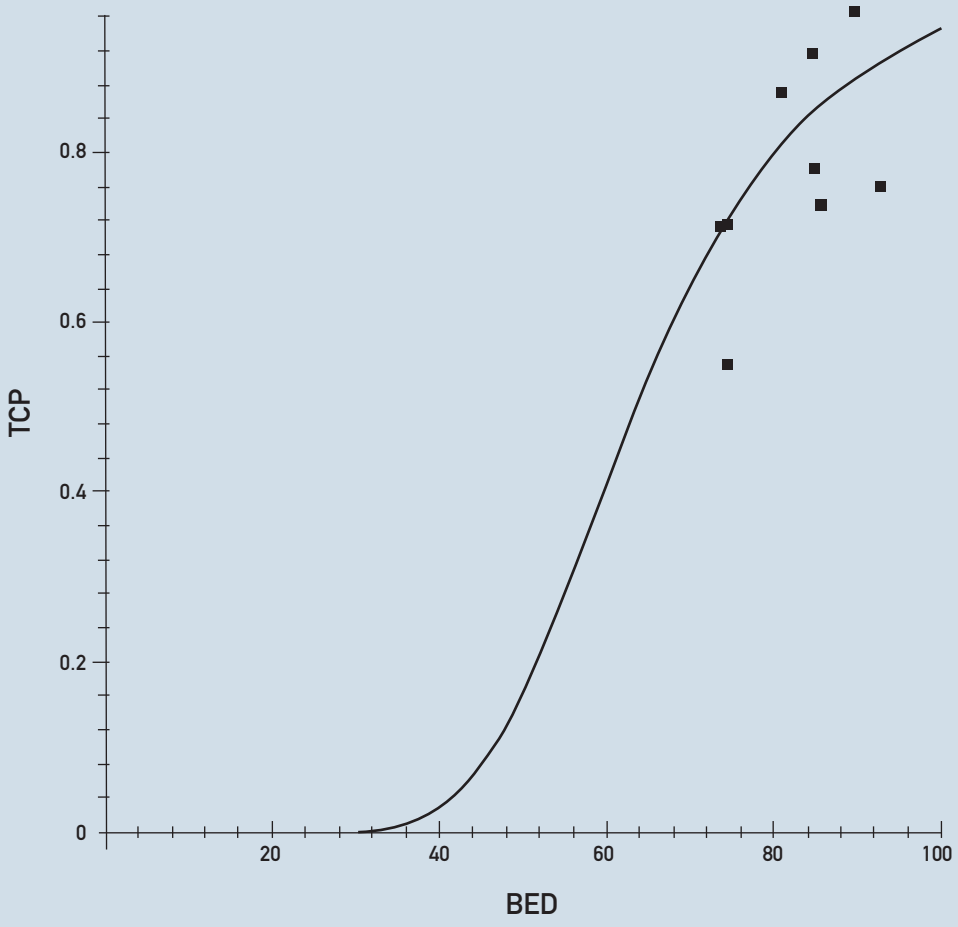
The optimal fractionation schedule for the postoperative RT of early breast cancer remains undefined and is a subject of wide variety in clinical practice. Yamada *et al.* [14] have reported that the BED values for two RT schedules (α/β =4Gy for breast cancer cells) are: 40Gy /16fr., BED=65Gy_4, and 50Gy/25fr. BED=75Gy_4. The 5-year local recurrence rates were 12.7% vs. 6.8%, respectively. They concluded that the latter fractionation schedule offers a smaller local recurrence rate of 6.8% vs. 12.7% that was obtained with the 40Gy /16fr., i.e. a relative difference of (12.7-6.8)/12.7 = 46.5%. This difference was not statistically significant (p=0.09).

However, our current study is suggestive of a plateau in TCP after nearly a BED of 90-100Gy_4. It is noteworthy that in a recent RCT by the EORTC (European Organization of Research and Treatment of Cancer) 251 initial-stage breast cancer patients with positive surgical margins after tumourectomy, received whole breast RT of 50Gy/25 fractions (BED=75Gy_4) and were randomised to either a boost of 10Gy (total BED=90Gy_4) or a boost of 26Gy (total BED=114Gy_4). Although this study was of a rather low power (37 "events" / local recurrences) its results are suggestive of a plateau in TCP after a RT with a BED of higher than 90Gy_4 [31].

Estimates of alpha and beta coefficients, such as the ones attempted in the present study, would probably contribute

Figure 3.

The calculated BED-TCP sigmoid curve based on data extracted from randomised trials of RT vs. no RT after tumourectomy for early-stage breast cancer. Each spot corresponds to a randomised clinical trial.



to more efficient reporting and comparisons of isoeffective doses of various fractionation schedules employed in accelerated partial breast RT. For example, a commonly used fractionation schedule for partial breast RT is 34Gy in 10 fractions over 5 days (RT given twice daily) [10]. This schedule gives a BED=63Gy$_4$, (with incomplete repair between fractions not taken into account -otherwise BED would be somewhat higher- Ref. 17). This, according to Figure 3, corresponds to a TCP of approximately 50%, meaning that a failure rate without RT of, i.e. 20%, would become approximately 10% after this RT schedule. This, according to our model, corresponds to a TCP of around 50%, which means that a failure rate without RT of, e.g. 20%, would become approximately 10% after this RT schedule.

The clinical use of any breast RT schedule would be an issue of further judgement based on a number of factors that would influence clinical decision. Those factors are TCP, normal tissue post-radiation effects, social and economic factors and healthcare resources. Models such as the one proposed in the present study could offer clinical guidance and guidance for the planning and assessment of clinical trials on adjuvant breast radiotherapy.

Hypofractionated breast radiotherapy

Radiation oncologists outside the UK and Canada are generally sceptical about using a RT regime with a higher-than-standard (1.8-2Gy) dose per fraction. However, this has more to do with personal judgment rather than with clinical data and radiobiological analysis. One of the main principles of radiobiology is that the late effects of normal tissues are strongly dependent on the size of dose per fraction, so that the higher the dose per fraction the greater the susceptibility of healthy tissues to radiation. This is known as "fractionation sensitivity". Fractionation sensitivity of tissues is quantified in terms of linear-quadratic (LQ) isoeffect formulation, by the α/β ratio [17, 32]; the higher the sensitivity to the size of dose per fraction, the lower the α/β ratio is. Late reacting normal tissues (connective tissue, neural tissue, etc.) have an α/β ratio of about 1.5-3Gy. Late post-radiation effects of breast are fibrosis, oedema, tenderness, telangiectasia and a combination of these effects, in addition to impaired cosmesis and have an α/β =3Gy. It should be mentioned that this discussion on hypofractionation does not apply to treatment of lymphatic pathways due to the very high fractionation sensitivity of the brachial plexus (neural tissue). Acute radiation reactions in normal tissues such as the skin or mucosa and squamous-cell carcinomas have an α/β ratio of 10Gy. It has been shown (see above) by radiobiological analysis of clinical data [5, 6, 16, 17, 32] that breast adenocarcinomas have an α/β ratio of around 4Gy, i.e. close to late reacting normal tissues. Consequently, hypofractionation in breast cancer may have a reasonable radiobiological background as more tumour cells will be killed by a high dose per fraction compared with the conventional 2Gy per fraction, and would potentially compensate for repopulation of tumour cells during RT. On the other hand, post-RT reactions and side-effects are not worse, or might be a bit better as START trials suggested, compared to standard RT schedules.

Radiotherapy equipment: a vital final note

An important tool in the safe implementation of hypofractionated RT in early breast cancer is proper equipment. Three-dimensional treatment planning allows for the distribution of the prescribed dose in the breast and normal tissues to be evaluated. In a randomised trial from the Royal Marsden Hospital, three-dimensional (3D) IMRT Intensity Modulated RT) against 2D dosimetry using standard wedge compensators, were compared regarding late reactions after whole breast RT. The 2D-arm patients were 1.7 times more likely to have a change in breast appearance than the IMRT-arm patients (p=0.008). Significantly fewer patients in the 3D IMRT group developed palpable breast induration [33].

Another technique that could make breast RT courses shorter is the accelerated partial breast irradiation (APBI), which is defined as a radiation technique that employs fractions higher than 1.8-2.0Gy per day to a partial volume of the breast over a period of less than 5-6 weeks. The rationale of this technique is to treat the lumpectomy cavity and an adjacent margin of 1-2cm as the majority of breast recurrences are diagnosed within this volume. The techniques for APBI demand for a specific and high-tech equipment and include interstitial implantation of radioactive needles, MammoSite *(the MammoSite system employs a dual lumen spherical balloon-catheter which is placed in the surgical cavity and filled with water; a high-dose-rate Iridium-192 source in the central lumen delivers the RT in 10 fractions over 5 days)*, targeted intraoperative therapy, intraoperative electrons and photon beams with 3D conformal/IMRT techniques [34]. The Intensity Modulated Partial Organ Radiotherapy (IMPORT) trial is a randomised trial, currently in progress in the UK, testing intensity modulated RT (IMRT) and partial organ RT following breast-conserving surgery for early breast cancer [35].

Modern equipment, although apparently expensive, offers now more than ever the opportunity to exploit the principles of clinical radiobiology and make Radiotherapy a cost-effective treatment modality. This could be a useful guidance for hospital managers in clinical oncology and is the current trend in the NHS (National Health Service) in the UK.

Note: The present work was partially based on our previous work with Prof Roger Dale, from Imperial College Healthcare NHS Trust London UK, published recently: Plataniotis GA, Dale RG. Int J Radiat Oncol Biol Phys 2009; 75:512-517.

Conflict of interest statement

The author declares no conflict of interest.

REFERENCES

1. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. Jour National Cancer Institute 2002; 94:1143-1150.
2. Magee B, Swindell R, Harris M, Banerjee SS. Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: results from a randomised trial. Radiother Oncol 1996; 39:223-227.
3. Ribeiro GG, Magee B, Swindell R, et al. The Christie Hospital Breast conservation trial: an update at 8 years from inception. Clin Oncol 1993; 5:278-283.
4. McBain CA, Young EA, Swindell R, Magee B, Stewart AL. Local recurrence of breast cancer following surgery and radiotherapy: incidence and outcome. Clin Oncol 2003; 15:25-31.
5. The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol 2008; 9:331-341.
6. The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet 2008; 371:1098-107.
7. Baillet F, Housset M, Maylin C, et al. The use of a specific hypofractionated radiation therapy regimen versus classical fractionation in the treatment of breast cancer: A randomized study of 230 patients. Int J Radiat Oncol Biol Phys 1999; 19:1131-1133.
8. Olivotto IA, Weir LM, Kim-Sing C, et al. Late cosmetic results of short fractionation for breast conservation. Radiother Oncol 1996; 41:7-13.
9. Shelley W, Brundage M, Hayter C. A shorter fractionation schedule for postlumpectomy breast cancer patients. Int J Radiat Oncol Biol Phys 2000; 47:1219-1228.
10. Bovi J, Qi XS, Li XA. Comparison of three accelerated partial breast irradiation techniques: treatment effectiveness based upon biological models. Radiother Oncol 2007; 84:226-232.
11. Offersena BV, Overgaard M, Kroman N and Overgaard J. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: A systematic review. Radiother Oncol 2009; 90:1-13.
12. Yarnold J, Bloomfield D, LeVay J, et al. Prospective randomised trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in women with early breast cancer (FAST) trial. Clin Oncol 2004; 16:S30.
13. Martin S, M. Mannino M, Rostom A, et al. Acute toxicity and 2-year adverse effects of 30 Gy in five fractions over 15 days to whole breast after local excision of early breast cancer. Clinical Oncology 2008; 20:502-505.
14. Plataniotis GA. Hypofractionated radiotherapy in the treatment of early breast cancer. World J Radiol 2010 June 28; 2(6):197-202.
15. Plataniotis GA, Theofanopoulou MA, Sotiriadou K, Kyrgias G. Hypofractionated radiotherapy for breast cancer patients treated by breast-conserving surgery: short-term morbidity and preliminary results. Breast Cancer 2010; 17:42-47.
16. Yamada Y, Ackerman I, Franssen E, et al. Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer? Int J Radiat Oncol Biol Phys 1999; 44:99-104.
17. Plataniotis GA. The principles of radiobiological modeling in radiotherapy. The use of models in clinical practice. Thesis in Radiation Oncology, University of Athens, Dept of Radiology. Athens 1992.
18. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomised clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985; 312:665-673.
19. Liljegren G, Holmberg L, Bergh J, et al. 10-year results after sector resection with or without postoperative radiotherapy for stage 1 breast cancer: A randomized trial. J Clin Oncol 1999; 17:2326-2333.
20. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: An update. J Natl Cancer Inst 1996; 88:1659-1664.
21. Veronesi U, Marubini E, Mariani L, et al. Radiotherapy after breast-conserving surgery in women with localized cancer of the breast. N Engl J Med 1993; 328:1587-1591.
22. Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Lancet 1996; 348:708-713.
23. Holli K, Saaristo R, Isola J, et al. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: Results of a randomized study. Br J Cancer 2001; 84:164-169.
24. Malstrom P, Holmberg L, Anderson H, et al. Breast conservation surgery, with and without radiotherapy, in women with lymph node-negative breast cancer: A randomized clinical trial in a population with access to public mammography screening. Eur J Cancer 2003; 39:1690-1697.
25. Hughes KS, Schnapper LA, Berry D, et al. Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. N Engl J Med 2004; 351:971-977.
26. Fyles AW, McCready DR, Manchul LA, et al. Tamoxifen with or without breast irradiation in women 50 years of age or older with early breast cancer. N Engl J Med 2004; 351:963-970.
27. Withers HR, Peters LJ, Taylor JMG. Dose-response relationship for radiation therapy of subclinical disease. Int J Radiat Oncol Biol Phys 1995; 31:353-359.
28. Kirkpatrick JP, Marks LB. Modeling killing and repopulation kinetics of subclinical cancer: direct calculations from clinical data. Int J Radiation Oncology Biol Phys 2004; 58:641-654.
29. Jack Y, Yang JY, Niemierko A, Yang MQ, Deng Y. Analyzing adjuvant radiotherapy suggests a non monotonic radio-sensitivity over tumor volumes. BMC Genomics 2008; 9(Suppl. 2):S9. doi:10.1186/1471-2164-9-S2-S9.
30. Hendry JH, West CM, Moore JV, and Potten CS. Tumour stem cells: the relevance of predictive assays for tumour control after radiotherapy. Radiother Oncol 1994 Jan; 30(1):11-6.
31. Poortmans PM, Collette L, Horiot JC, et al.; on behalf of the EORTC Radiation Oncology and Breast Cancer Groups. Impact of the boost dose of 10 Gy versus 26 Gy in patients with early stage breast cancer after a microscopically incomplete lumpectomy: 10-year results of the randomised EORTC boost trial. Radiother Oncol 2009; 90:80-85.
32. Plataniotis GA. Clinical Radiobiology. The action of ionizing radiation in biological material. University Studio Press, Thessalonica 2000 (in Greek).
33. Donovan E, Bleakley N, Denholm E, et al. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. Radiother Oncol 2007; 82:254-264.
34. Mannino M, Yarnold J. Accelerated partial breast irradiation trials: diversity in rationale and design. Radiother Oncol 2009; 91:16-22.
35. Institute of Cancer Research. Visited on September 4, 2010. Available from: URL: http://www.icr.ac.uk/research/research_sections/clinical_trials/clinical_ trials_list/10284. shtml.

Do concurrent chemoradiotherapy with docetaxel followed by docetaxel consolidation chemotherapy improve the outcome of anaplastic thyroid carcinoma patients?

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ABSTRACT

Background: Anaplastic thyroid cancers (ATC) are undifferentiated tumors of the thyroid follicular epithelium which are extremely aggressive, with a disease-specific mortality approaching 100 percent. A standardized successful protocol remains to be established and the optimal sequence of multimodal therapy is still on debate.

This study was designed to evaluate the efficacy of concurrent chemoradiotherapy with docetaxel in anaplastic thyroid carcinoma (ATC).

Patients & Methods: Eighteen ATC patients were enrolled into this study. They were first treated with surgical debulking of the tumor if possible, followed by concurrent chemoradiotherapy with docetaxel, conventionally fractionated radiation (60Gy in 2Gy fractions) to the gross or residual primary disease and regionally involved lymph nodes was given, followed by 4 cycles of docetaxel as consolidation chemotherapy in cases with no evidence of progression.

Results: Two patients (11.11%) had complete response (CR); nine patients (50%) achieved partial response (PR); one patient (5.56%) remained stable; while disease progression was observed in 6 patients (33.33%). The median overall and progression-free survival times were 7 [95% CI, 5.62-8.38] and 4 [95% CI, 2.62-5.38] months, respectively. Almost all patients had Grade I- II dysphagia, while only three patients (16.67%) had Grade III. Hematological toxicity was relatively mild where Grade I anemia and neutropenia were detected in 5 and 6 patients, respectively, while Grade II was detected in 3 and 2 patients, respectively.

Conclusions: This study showed that docetaxel concurrent with radiotherapy followed by consolidation docetaxel is feasible and effective in patients with ATC.

Key words: anaplastic thyroid carcinoma; concurrent chemoradiotherapy; docetaxel; multimodal therapy.

INTRODUCTION

Anaplastic thyroid cancers (ATC) are undifferentiated tumors of the thyroid follicular epithelium. In marked contrast to differentiated thyroid cancers, anaplastic cancers are extremely aggressive, with a disease-specific mortality approaching 100 percent [1].

The annual incidence of anaplastic cancer is about two per million persons [2, 3] and accounts for only 2 to 5 percent of all thyroid cancers. Patients with anaplastic cancer are older than those with differentiated cancer; the mean age at diagnosis is 65 years and less than 10 percent are younger than 50 years. Sixty to 70 percent of tumors occur in women [4].

Approximately 20 percent of patients with anaplastic thyroid cancer have a history of differentiated thyroid cancer, and 20 to 30 percent have a coexisting differentiated cancer [5].

Due to its dismal prognosis, there have been different kinds of treatment modalities to improve patient survival. The first treatment option is to perform palliative surgeries of the thyroid cancer, in order to reduce tumor burden, however, many patients present with an inoperable disease, and complete resection is possible for only up to one-third of patients at presentation [5]. After surgery, either radiotherapy or chemotherapy or both could be provided to prevent tumor progression and further distant metastasis [6].

Nevertheless, the aggressive nature and rarity of ATCs make it difficult to compare patient outcomes, especially in studies with small cohorts and short follow-up [7].

Doxorubicin is the most commonly used chemotherapy shown to have efficacy against ATC as a radiosensitizing agent, [8-11] but failed to show any significant improvement compared with monotherapy in *in vitro* studies [12, 13]. In an early study, external-beam radiation therapy alone or in conjunction with doxorubicin radiosensitization did not show any improvement in overall survival [5].

Docetaxel has reported a clinical efficacy against ATC, with a promising survival therapy when compared to the current reported median survival time of 5-6 months without treatment [14, 15, 16].

This prospective study was conducted on patients with anaplastic thyroid carcinoma (ATC) to study the efficacy of concurrent docetaxel chemoradiotherapy followed by consolidation docetaxel.

PATIENTS & METHODS

This prospective study was carried out in the oncology center, Clinical Oncology and Nuclear Medicine Department, Mansoura University, Egypt, in the period from January 2009 to June 2012; it included 18 patients pathologically confirmed to have anaplastic thyroid carcinoma treated with maximal debulking surgery followed by external radiotherapy combined with docetaxel chemotherapy.

Patients older than 20 years were eligible for this study if they had pathologically confirmed ATC, no prior chemotherapy, with measurable lesion that could be assessed according to the Response Evaluation Criteria In Solid Tumors (RECIST) [17].

Before treatment initiation, all patients underwent a computed tomography scan of the neck, as well as of thorax and abdomen, and additional sonography and magnetic resonance imaging was performed in individual cases.

Surgery

Maximal debulking of all resectable gross tumor including thyroid and cervical nodes was performed to control local symptoms of neck mass or impending tracheal obstruction.

Treatment plan

All patients received standard external beam RT, a dose of 45Gy in 23 fractions to the neck and upper mediastinum (given by 2-field anterior-posterior opposed photon fields, extending from the tips of mastoid processes down to the carina), followed by boost to the thyroid bed and any residual disease to a total of 60Gy.

Radiotherapy was delivered with linear accelerator (6MV photon).

Chemotherapy and radiotherapy began simultaneously. Docetaxel was given intravenously in a dose of 20mg/m^2/day on days 1, 8, 15, 22, 29 and 36. The chemotherapy was given at approximately 30-60 minutes before receiving radiotherapy.

Patients were required to have absolute neutrophil count ≥1500/μL without evidence of active infection, platelet count ≥100000/μL, Hb >9gram/dl, liver function; AST, ALT <2x upper normal limit (UNL), total bilirubin <or equal 1.5x UNL, renal function; serum creatinine <2mg/dl and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Restaging was performed 6 weeks after chemoradiotherapy and consisted of imaging of all tumoral sites documented before therapy initiation. Assessment of response was performed according to the RECIST criteria.

In the absence of clinical or radiological evidence of progressive disease, consolidation docetaxel started 6 weeks after chemoradiotherapy at 60mg/m^2 intravenously over 1 hour every 21 days for 4 cycles. Chemotherapy was administered only if the ANC was ≥1500/uL, Hb >9 gram/dl and platelet count was ≥100,000/uL. Otherwise, treatment was delayed for one week to allow hematological recovery.

Evaluation of response and toxicity

Each patient underwent baseline evaluations, including a complete physical examination, CT and/or MRI of the target lesion. Tumor response was evaluated by clinical examination, neck CT scan or MRI 4 to 6 weeks after chemoradiotherapy. Patients were followed by imaging study with CT scan or MRI every three months. Based on the Response Evaluation Criteria In Solid Tumor, responses were assessed and categorized as complete response, partial response, stable disease, and progressive disease [17].

Radiation-related toxicities were graded according to the Radiation Morbidity Scoring Criteria of the Radiation Therapy Oncology Group (RTOG) [18], while chemotherapy toxicity was recorded according to the National Cancer Institute Common Toxicity Criteria (version 3.0) [19].

Endpoints

The primary endpoints were tumor response and survival, whereas the secondary endpoint was treatment toxicity.

Statistical analysis

The statistical analysis of data was conducted using the SPSS program for MS Windows version 17. The descriptive data was delivered in the form of median ± SE for quantitative data; and frequency and proportion for qualitative data. Time to progression-free survival (PFS) and overall survival were determined using the Kaplan-Meier method to provide the median value and 95% CI. Survival curves were calculated from life tables.

RESULTS

Between January 2009 and June 2012, a total of eighteen female patients were enrolled into this study (Table 1). The median age was 65 years (range, 55 - 74). Most patients (67%) had Eastern Cooperative Oncology Group (ECOG) performance status 2. Most of them presented with unre-

sectable primary tumor (T4b 72%) and regional nodal involvement (N1a 39%, N1b 61%). Debulking surgery was performed for all patients.

All patients had completed their course of chemoradiotherapy except three; 2 of them died during treatment after receiving 48Gy and 52Gy, respectively, while the third received 54Gy.

The treatment outcomes of patients treated with concomitant chemoradiotherapy (CCRT) were as follows: six patients had progressive disease (33.33%), two of them (11.11%) died during treatment, one due to airway obstruction because of disease progression and the other died of aspiration pneumonia during CCRT. Ten patients (55.56%) achieved objective response; two had (11.11%) complete response (CR); and the other eight (44.45%) achieved partial response (PR). Two patients (11.11%) showed stable disease (Table 2).

Patients who expressed non-progressive disease received consolidation chemotherapy, docetaxel 60mg/m^2 every 3 weeks. The range of administered treatment cycles was 1 - 4. At the end of the treatment, the local control was assessed, where eleven patients (61.11%) achieved objective response [CR 2(11.11%), PR 9 (50%)] and only one patient (5.56%) remained radiologically stable.

The median overall and progression-free survival were 7 [95% CI, 5.62-8.38] and 4 months [95% CI, 2.62-5.38], respectively, whereas the mean overall and progression-free survival were 8.2 [95% CI, 6.09-10.38] and 6 [95% CI, 3.93-8.07] months, respectively (Figures 1, 2).

Regarding side-effects during CCRT, hematological toxicity was relatively mild where Grade I anemia and neutropenia were detected in 5 and 6 patients, respectively; while Grade II was detected in 3 and 2 patients, respectively. Almost all patients had Grade I-II dysphagia, while only three patients (16.67%) had Grade III and required hospitalization for parenteral nutrition and fluid replacement. One patient developed aspiration pneumonia during CCRT requiring parenteral antibiotics and died from respiratory distress. Mild vomiting was only detected in four patients (Table 3).

Table 1.

Patient characteristics.

Patient characteristics	No of patients = 18	Percent = 100%
Sex		
Female	18	100%
Age (years)		
Median	65	
Range	55 - 74	
ECOG performance status		
1	6	33%
2	12	67%
Stage of primary tumor*		
T4a	5	28%
T4b	13	72%
Nodal stage*		
N0	0	0%
N1a	7	39%
N1b	11	61%
Overall stage of disease*		
IV a	4	22%
IV b	14	78%

**Tumor and nodal disease extent based on the 6th edition of the American Joint Committee Cancer Staging Manual.*

Table 2.

Tumor response to concurrent chemoradiotherapy.

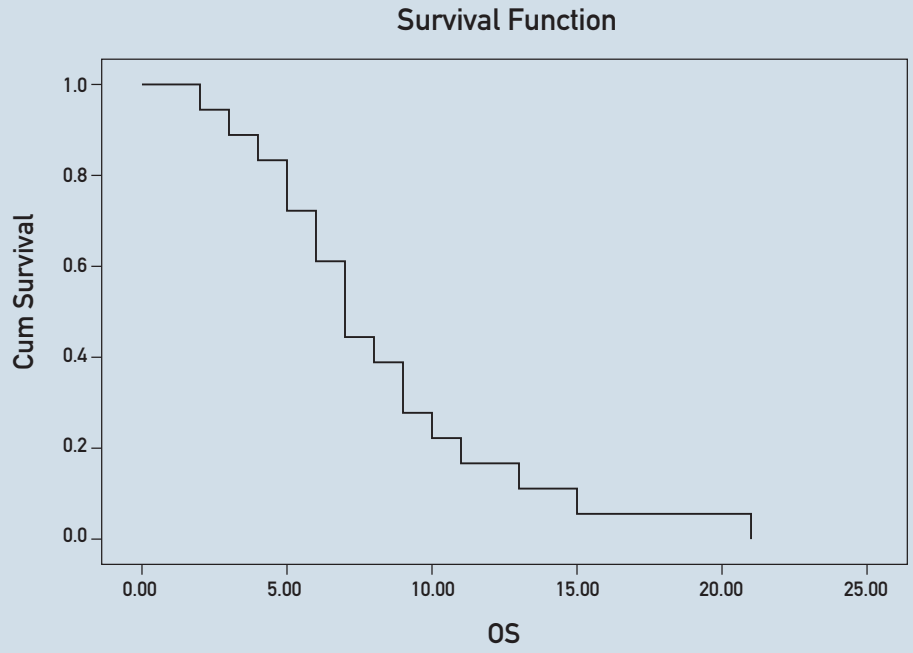
Response	No	%
Complete response	2	11.11
Partial response	8	44.45
Stable disease	2	11.11
Progressive disease	6	33.33

Table 3.

Chemoradiotherapy-related toxicity.

Toxicities	Grade I		Grade II		Grade III		Grade IV	
	No	%	No	%	No	%	No	%
Hematological								
Anemia	5	27.78	3	16.67	0	0	0	0
Neutropenia	6	33.34	2	11.11	0	0	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0
Non-hematological								
Dysphagia	8	44.44	7	38.89	3	16.67	0	0
Vomiting	4	22.22	0	0	0	0	0	0
Dermatitis	5	27.78	2	11.11	0	0	0	0

Figure 1.
Overall survival.



Radiation dermatitis was mainly confined to irradiated fields. The irradiated skin showed various degrees of erythema with hyperpigmentation. Five patients experienced Grade I radiation dermatitis with only 2 patients developing moist skin desquamation towards the end of treatment. All acute reactions had completely subsided three to five weeks after treatment completion.

During consolidation chemotherapy, myelosuppression - especially neutropenia- was common, where 5 (41.67%) patients had Grade I neutropenia; while 3 patients (25%) developed Grade II. Grade I and II anemia were found in 4 (33.33%) and 2 (16.67%) patients, respectively, while Grade I thrombocytopenia was recorded in three patients (25%). No Grade III or IV toxicity was detected.

DISCUSSION

Anaplastic thyroid cancer (ATC) is one of the most aggressive solid tumors that affect humans, with a median survival in the order of 5 to 6 months following diagnosis with a 1-year survival rate of about 10% [20].

Management of ATC is particularly difficult because patients usually present with both extensive local disease and distant metastases and the tumor often grows during treatment and the cause of death for most patients is local tumor invasion [21], so a standardized successful protocol remains to be established and the optimal sequence of multimodal therapy is still on debate [7].

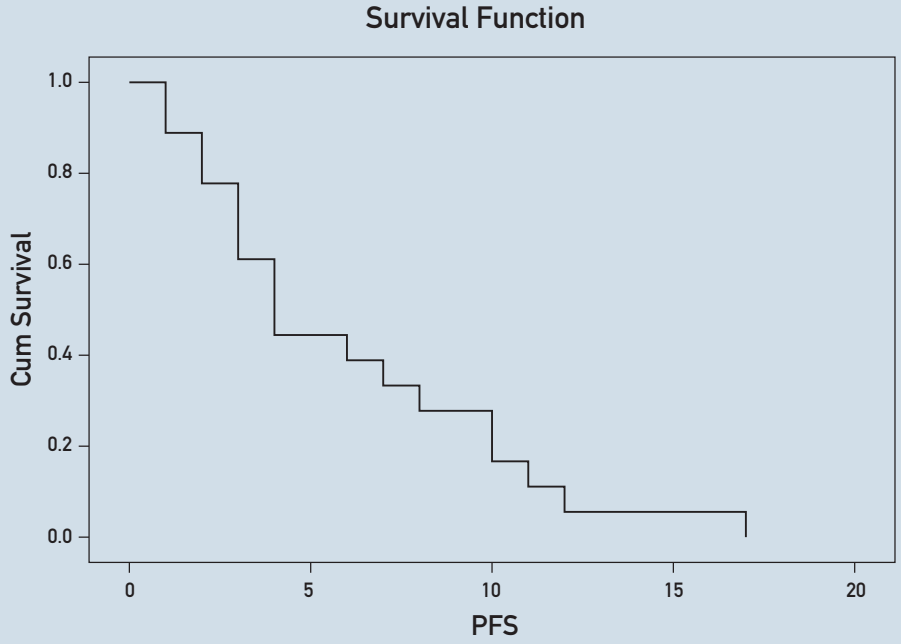
In a study from Serbia, 16 inoperable ATC patients were treated with radiotherapy at 60Gy, followed by doxorubicin 60mg/m^2 and cisplatin 40mg/m^2 every 3 weeks. The overall response rate (ORR) was 25% (95% CI: 7-55). No toxic deaths occurred or Grade 4 adverse events were reported after radiotherapy. Grade 4 toxicity was seen in 3 patients after chemotherapy. Median OS was 11.0 months (95% CI: 8.56-13.44) [22].

A study from the Netherlands reported significantly improved local control and improved median survival with a protocol consisting of locoregional radiotherapy in 46 fractions of 1.1Gy, given twice daily, followed by prophylactic irradiation of the lungs in 5 daily fractions of 1.5Gy. Low-dose doxorubicin (15mg/m^2) is administered weekly during radiotherapy, followed by adjuvant doxorubicin (50mg/m^2) 3-weekly up to a cumulative dose of 550mg/m^2 [9].

A recent study by Troch *et al.* [14] showed high efficacy of concomitant treatment with docetaxel and radiation. They performed a retrospective analysis of six patients with ATC using docetaxel and external beam radiation, standard external beam radiation of 60Gy was combined along with docetaxel at 100mg fixed dose every 3 weeks for a total of six cycles starting within the first week of radiation. The results were remarkable, with only one patient having completed radiation at the time of the report. Four patients achieved complete remission and two partial response. After a median follow up of 21.5 months (range, 2-40 months), five patients were alive [14].

A prospective feasibility study at a single center included 7

Figure 2.
Progression-free survival.



patients with anaplastic thyroid cancer who had received no prior chemotherapy. They received docetaxel intravenously at a dose of 60mg/m^2 over the course of 1h every 3 weeks. Treatment response was complete response in one patient, stable disease in two and progressive disease in four. The response rate was 14%, and the median time to progression was 6 weeks (range, 1-50). Toxicity was tolerable [15].

In a prospective phase II study that included 13 ATC patients, treated first with surgical debulking of the tumor if possible, then concomitant chemoradiation with docetaxel, cisplatin (TP regimen), conventionally fractionated radiation (60Gy in 2Gy fractions) to the gross or residual primary disease and regionally involved lymph nodes was given, followed by 4 cycles of consolidation chemotherapy (TP regimen) / 3 weeks.

The median survival was 16.8 months. After concomitant chemoradiation, 7 patients (53.8%) achieved objective response. Neutropenia (23%), anemia (15.3%), nausea and vomiting (15.3%) and pharyngo-esophagitis (7.6%) were the most severe Grade 3 and 4 acute toxicities recorded during concomitant chemoradiation. Neutropenia (30.7%) and anemia (23%) were the most pronounced Grade 3 and 4 toxicities during consolidation chemotherapy [23].

Another study has shown promising results with the combination of docetaxel, doxorubicin and radiation, where median survival was 40 months, with 60% alive at 2 years, but most patients were hospitalized for severe mucositis or infection [24].

A retrospective review study at a single referral center included 100 patients with a diagnosis of ATC, where seventy-eight patients received radiotherapy, with 58 receiving a total dose of ≥40Gy. Twenty-seven patients received chemotherapy, and 15 patients received multimodal therapy (surgery, radiotherapy and chemotherapy). Survival rates by stage at 1 year were 72.7% (stage IVA), 24.8% (stage IVB,) and 8.2% (stage IVC) [25].

In a recently published retrospective review of the medical records of 13 anaplastic thyroid cancer patients who were treated at a single center and received multidisciplinary treatment, five patients received doxorubicin-based definitive concurrent chemoradiotherapy (CCRT), and eight received surgery followed by postoperative RT or CCRT. The median progression-free survival and overall survival were 2.8 months (95% CI, 1.2-4.4 months) and 3.8 months (95% CI, 3.0-4.6 months), respectively. After CCRT, only one patient's condition remained stable, and rapid disease progression was observed in the other four patients [26].

A retrospective study reviewed 44 ATC patients treated with total thyroidectomy and cervical lymph-node dissection, when feasible, combined with 2 cycles of doxorubicin (60mg/m^2) and cisplatin (100mg/m^2) every 3 weeks, hyperfractionated (1.2Gy, twice daily) radiation to the neck and upper mediastinum (46-50Gy), and then four cycles of doxorubicin-cisplatin. Complete response after treatment was achieved in 14/44 patients (31.8%). Eight patients had a partial response (18.2%). Twenty-two (50%) had progressive disease. Thirteen patients are still alive. Median survival of the entire population was 8 months [27].

Our results compared favorably with the results of other series of concomitant chemoradiation [14, 15, 22, 26, 27], whereas they were inferior in comparison to others [23, 24] which may be explained by the use of combined chemotherapeutic agents concurrently with radiotherapy.

In a phase II study by Savvides *et al.*, they assessed the efficacy and toxicity of sorafenib in 16 pretreated patients with anaplastic thyroid carcinoma, where disease control rate (stable disease and partial response) was 40% and toxicity was manageable [28].

So, sorafenib demonstrates an acceptable response rate in anaplastic thyroid carcinoma and further clinical trials are warranted, but due to the rarity of this tumor such a trial will be hard to accomplish [29].

Also, the combination of pazopanib with microtubule inhibitors such as paclitaxel produced synergistic antitumor effects in ATC cells. These combined effects may reflect enhanced paclitaxel-induced cytotoxicity mediated by cell cycle regulatory kinase inhibition by pazopanib. These results suggest that the pazopanib/paclitaxel combination is a promising candidate therapeutic approach in ATC [30].

CONCLUSION

Preliminary results from this study show that docetaxel concurrent chemoradiotherapy followed by consolidation docetaxel is feasible and effective in patients with ATC and that larger trials are warranted in order to judge the efficacy of this combined approach. Further prospective multicenter clinical trials are needed to elucidate an effective mode of treatment.

Conflict of interest statement

The authors declare no conflict of interest.

REFERENCES

1. Neff RL, Farrar WB, Kloos RT, Burman KD. Anaplastic thyroid cancer. Endocrinol Metab Clin North Am 2008; 37:525.
2. Mazzaferri EL. Undifferentiated thyroid carcinoma and unusual thyroid malignancies. In: Endocrine Tumors, Mazzaferri EL, Samaan NA (Eds), Blackwell Scientific Publications, Boston 1993, p. 378.
3. Akslen LA, Haldorsen T, Thoresen SO, Glattre E. Incidence of thyroid cancer in Norway 1970-1985. Population review on time trend, sex, age, histological type and tumour stage in 2625 cases. APMIS 1990; 98:549.
4. Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A. Anaplastic thyroid carcinoma. Treatment outcome and prognostic factors. Cancer 2005; 103:1330.
5. McIver B, Hay ID, Giuffrida DF, et al. Anaplastic thyroid carcinoma: a 50-year experience at a single institution. Surgery 2001; 130:1028-34.
6. Pierie JP, Muzikansky A, Gaz RD, Faquin WC, Ott MJ. The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. Ann Surg Oncol 2002; 9:57-64.
7. Kihara M, Miyauchi A, Yamauchi A, Yokomise H. Prognostic factors of anaplastic thyroid carcinoma. Surg Today 2004; 34:394-398.
8. Siironen P, Hagstrom J, Maenpaa HO, et al. Anaplastic and poorly differentiated thyroid carcinoma: therapeutic strategies and treatment outcome of 52 consecutive patients. Oncology 2010; 79(5-6):400-408.
9. Swaak-Kragten AT, de Wilt JH, Schmitz PI, Bontenbal M, Levendag PC. Multimodality treatment for anaplastic thyroid carcinoma - treatment outcome in 75 patients. Radiother Oncol 2009; 92(1):100-104.
10. Haigh PI, Ituarte PH, Wu HS, et al. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer 2001; 91(12):2335-2342.
11. Pudney D, Lau H, Ruether JD, Falck V. Clinical experience of the multimodality management of anaplastic thyroid cancer and literature review. Thyroid 2007; 17(12):1243-1250.
12. Kim TY, Kim KW, Jung TS, et al. Prognostic factors for Korean patients with anaplastic thyroid carcinoma. Head Neck 2007; 29(8):765-772.
13. Zheng X, Cui D, Xu S, Brabant G, Derwahl M. Doxorubicin fails to eradicate cancer stem cells derived from anaplastic thyroid carcinoma cells: characterization of resistant cells. Int J Oncol 2010; 37(2):307-315.
14. Troch M, Koperek O, Scheuba C, et al. High efficacy of concomitant treatment of undif-ferentiated (anaplastic) thyroid cancer with radiation and docetaxel. J Clin Endocrinol Metab 2010; 95:E54-7.
15. Kawada K, Kitagawa K, Kamei S, et al. The feasibility study of docetaxel in patients with anaplastic thyroid cancer. Jpn J Clin Oncol 2010; 40(6):596-599.
16. Kurukahvecioglu O, Ege B, Poyraz A, Tezel E, Taneri F. Anaplastic thyroid carcinoma with long term survival after combined treatment: case report. Endocr Regul 2007; 41(1):41-44.
17. Eisenhauer EA, Therasse P, Bogaerts J, et al. 2009 New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228-247.
18. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). Int J Rad Oncol Biol Phys 1995; 31:1341-6.
19. Cancer Therapy Evaluation Program. Common toxicity criteria, version 3.0. DCTD, NCI, NIH, DHHS. March 31, 2003 (http://ctep.cancer.gov), Publish Date: August 9, 2006.
20. Smallridge RC, Copland JA. Anaplastic thyroid carcinoma: pathogenesis and emerging therapies. Clin Oncol 2010; 22(6):486-497.
21. Are C, Shaha AR. Anaplastic thyroid carcinoma: biology, pathogenesis, prognostic factors and treatment approaches. Ann Surg Oncol 2006; 13(4):453-464.
22. Vrbic S, Pejcic I, Vrbic M, and Filipovic S. Therapy of stage IV B anaplastic thyroid carcinoma: single institution experience. Journal of Balkan Union of Oncology 2009; 14(1):41-44.
23. Abdel-Hakim KN. Concurrent chemoradiotherapy with docetaxel plus cisplatin (TP regimen) followed by consolidation chemotherapy with TP regimen in treatment of anaplastic thyroid cancer. Pan Arab Journal of Oncology 2011; 4(2).
24. Foote RL, Molina JR, Kasperbauer JL, et al. Enhanced survival in locoregionally confined anaplastic thyroid carcinoma: a single-institution experience using aggressive multimodal. Thyroid 2011; 21(1):25-30.
25. Akaishi J, Sugino K, Kitagawa W, et al. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. Thyroid 2011; 21:1183-9.
26. Min Lim S, Shin S, Chung W, et al. Treatment outcome of patients with anaplastic thyroid cancer: a single center experience. Yonsei Med J 2012; 53(2):352-357.
27. Derbel O, Limem S, Ségura-Ferlay C, et al. Results of combined treatment of anaplastic thyroid carcinoma (ATC). Cancer 2011; 11:469.
28. Savvides P, Nagaiah G, Lavertu PN, Fu P, et al. Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. Thyroid 2013; 23(5):600-604.
29. Zygulska A, Krzemieniecki K, Sowa-Staszczak A. The use of sorafenib in the thyroid cancer. European Endocrinology 2013; 9(1):28-31.
30. Isham C, Bossou A, Negron V, Fisher K, Kumar R, Marlow L, Lingle W, Smallridge R, Sherman E, Suman V, Copland J, and Bible K. Pazopanib enhances paclitaxel-induced mitotic catastrophe in anaplastic thyroid cancer. Sci Transl Med 2013 Jan; 5(166):166.

The importance of economic evaluation in healthcare decision-making – A case of denosumab versus zoledronic acid from Greece. Third-party payer perspective

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ABSTRACT

Background: Patients with bone metastases secondary to solid tumors frequently experience skeletal-related events (SREs). It is debatable whether the modest reduction in the rate of SREs observed with a recently approved monoclonal antibody, denosumab, outweighs financial implications associated with its relatively higher cost. In the current scenario of economic slowdown and concerns around increasing healthcare expenditure, economic evaluation is increasingly being utilized for healthcare decision-making. Here, we present an economic evaluation of denosumab versus zoledronic acid for the treatment of bone metastases secondary to solid tumors from a third-party payer perspective.

Patients & Methods: An Excel-based cost-effectiveness analysis including patients with bone metastases secondary to breast, prostate, or other solid tumors was performed. Efficacy and quality of life decrement inputs were based on the available literature; healthcare cost and resource utilization inputs were obtained from the Greek healthcare system. One-way sensitivity analysis was performed.

Results: In the base-case analysis, denosumab had an incremental cost per quality-adjusted life year of €56,818 for breast cancer; €61,296 for prostate cancer; and €80,830 for other solid tumors. Incremental costs per SREs avoided in relation to zoledronic acid were €3614, €4889, and €4854 for breast cancer, prostate cancer, and other solid tumors, respectively.

Conclusions: Economic analysis presents an opportunity to evaluate alternative options to facilitate decision-making and opt for the choice offering best value for money. At a threshold of €30,000, denosumab was not a cost-effective option for the prevention of SREs in patients with bone metastases secondary to solid tumors from a Greek third-party payer perspective.

Key words: bone metastases; cost-effectiveness; denosumab; skeletal-related events; zoledronic acid.

Abbreviations

CRPC, castration-resistant prostate cancer; DRG, diagnosis-related group; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; NSCLC, non-small-cell lung cancer; QALY, quality-adjusted life year; QoL, quality of life; RANKL, receptor activator of nuclear factor kappa-B ligand; SRE, skeletal-related events.

INTRODUCTION

Bone is one of the most common sites of distant metastases among patients with cancer. Although bone metastases remain a cause of considerable morbidity in patients with almost all tumor types, prostate, breast, and lung cancer are most frequently implicated [1, 2]. It is estimated that up to 75% of patients with advanced prostate or breast cancer, and around 40% patients with advanced lung cancer develop bone metastases [3]. Patients with bone metastases frequently experience osteoclast-mediated bone destruction and severe skeletal-related events (SREs) such as pathological fractures, spinal cord compression, hypercalcemia, and bone pain requiring radiotherapy and orthopedic surgery [4, 5]. Bone metastases and consequent SREs are associated with unfavorable prognosis, increased mortality, and decreas-

ed quality of life (QoL) in terms of mobility, independence, and social functioning [5, 6].

Considering the great morbidity associated with bone metastases, therapeutic management assumes high clinical importance [2]. The aim of treatment for bone metastases is to not only manage skeletal morbidity by delaying or preventing SREs but also to improve overall QoL. The different treatment options for patients with bone metastases include radiation therapy, analgesics, surgery, and bisphosphonates [7]. The latter provide relief from bone pain by inhibiting osteoclast activity, which induces pathological bone conditions in bone metastases, and consequently reducing the risk of fractures and other complications [8]. Zoledronic acid (Zometa®, Novartis), a bisphosphonate, is an approved bone-targeted pharmacological treatment to prevent SREs secondary to advanced solid tumors in patients with bone metastases [9].

Denosumab (Xgeva®, Amgen) is a human monoclonal antibody that inhibits osteoclast-mediated bone resorption by binding to the receptor activator of nuclear factor kappa-B ligand (RANKL) and prevents local bone destruction [10]. Data from three pivotal phase III, randomized controlled trials reveals that denosumab is more effective in reducing the incidence of SREs compared to zoledronic acid in patients with solid tumors [11-13]. In these studies, denosumab demonstrated a statistically significant and clinically meaningful improvement in preventing SREs compared to zoledronic acid in breast cancer [11]; prostate cancer [12]; and other solid tumors [13]. Subsequently, denosumab has been approved in Europe for the prevention of SREs in adults with solid tumors to prevent serious complications caused by bone metastases [14].

Greece, like other member States in the European Region, is facing a formidable financial crisis and many cost-containment measures have been implemented in all fiscal sectors, with health being one of them. In the healthcare sector the main emphasis is on the control of pharmaceutical prices and efforts are made to maximize value for money [15]. In an attempt for the Greek NHS to establish evidence-based prescribing behaviors, the introduction of positive lists has been implemented in pharmaceuticals in March 2013 with cost-effectiveness analysis as the main criterion for medicine categorization [16].

Cost-effectiveness analysis represents a robust methodology to quantify the relative benefits and costs of new treatments in comparison to standard-of-care options. Economic modeling provides essential information to determine which treatments generate more value for the money spent per patient. Cancer trials rarely collect enough data on treatment costs and consequences for rigorous economic assessment; thus, mathematical modeling is required to support decision-making [16]. It is debatable whether the modest reduction in the rate of SREs with denosumab, as has been observed in the head-to-head comparisons with zoledronic acid, outweighs financial implications associated with its relatively higher cost (nearly twice the cost of zoledronic acid in the USA) from a payer's perspective in order to consider denosumab as a new option for standard of care [18]. None of the studies compared the cost-effectiveness of denosumab versus zoledronic acid in patients with advanced solid tumor complicated with bone metastases in Greece. The aim of this study was, therefore, to perform a literature-based economic evaluation of denosumab versus zoledronic acid in patients with bone metastases secondary to breast cancer, prostate cancer, and other solid tumors.

METHODS

We adopted an Excel-based model developed by Lothgren *et al.* [19] to perform a cost-effectiveness analysis simulating the outcomes to reflect the Greek third-party payer perspective. In the model-based economic evaluation, Lothgren *et al.* compared denosumab with zoledronic acid for the prevention of SREs in patients with bone metastases in the Netherlands [19]. For our analysis, we used efficacy and QoL decrement inputs available from this model, and healthcare cost and resource utilization inputs from the Greek healthcare system. Specifically, for both interventions -denosumab and zoledronic acid- the costs associated with drug acquisition, administration, SREs, and patient monitoring were taken into account. Since economic consequences of treatments were evaluated from a third-party payer perspective, only direct medical costs were included. The time horizon of analysis was 22.5 months for breast cancer, 14.5 months for prostate cancer, and 9 months for other solid tumors. All analyses were performed using Microsoft Excel 2003.

Efficacy and QoL decrement inputs

For both the interventions, efficacy and QoL decrements associated with each SRE type and tumor type were obtained from the Lothgren *et al.* study [19]. In the model parameters of the Lothgren *et al.* study, probabilities of having each type of SRE and discontinuation rates of therapy were mainly extracted from the results of the three pivotal phase III clinical trials aimed at evaluating the efficacy of denosumab versus zoledronic acid for the prevention of SREs in solid tumor patients with bone metastases [11-13]. The trial-based annualized SRE-rates (first and subsequent SREs) for denosumab were 0.35, 0.47, and 0.55, and those for zoledronic acid were 0.45, 0.59, and 0.65 in breast cancer, prostate cancer, and other solid tumors, respectively. The relative distribution of SRE types by solid tumors was considered identical for both denosumab and zoledronic acid. The distribution of SRE types is presented in Table 1.

Further, owing to lack of data from clinical practice, discontinuation rates of therapy for the Lothgren *et al.* study were also obtained from published clinical trials [11-13]. Such trial-based discontinuation rates (per model cycle,

Table 1.
Distribution of SRE types.

SRE type	Breast	Prostate	Other solid tumors
Pathological fracture	64.50%	36.30%	35.60%
Radiation to the bone	29.40%	55.10%	51.30%
Surgery to the bone	3.80%	1.10%	6.40%
Spinal cord compression	2.30%	7.50%	6.70%
Total	100%	100%	100%

SRE, skeletal-related event.

denosumab vs. zoledronic acid) for breast cancer, prostate cancer, and other solid tumors were 0.0216 vs 0.0219; 0.0310 vs 0.0359; and 0.0465 vs 0.0472, respectively. The relative values for QoL decrements were identical for both denosumab and zoledronic acid (Table 2).

Healthcare cost and resource utilization inputs

For the base-case analysis, the drug acquisition cost of zoledronic acid was calculated based on the hospital price of €196 per 4mg vial (including 5% social insurance price) available from the latest price-bulletin issued by the Greek Ministry of Health, and excluded the value-added tax (as it represents a transfer price) [20]. As denosumab was not available in the market, a hypothetical price was considered. Based on the summary of product characteristics, the first injection of denosumab is to be delivered in the hospital, while the remaining injections are to be administered under the responsibility of a healthcare professional [14]. Therefore, another scenario was considered where denosumab was assumed to be obtained from community pharmacists except for the first one. For the base-case analysis, it was deemed that denosumab is obtained and reimbursed as a hospital-administered therapy by the pharmacy departments of the EOPYY (the main healthcare fund). For the sensitivity analysis, it was considered that denosumab is obtained and reimbursed from the community pharmacists (based on the following formula: [hospital price x 2% x 8%] + €30). In the third scenario, the price of generic zoledronic acid was set at €78.40 per vial (40% of the branded product price), as zoledronic acid is going off-patent in 2013. The drug acquisition cost of denosumab was calculated as €304.82 per 120mg (obtained from the April 2012 drug price bulletin) [21].

In our analysis, we also included administration cost for both interventions. The administration cost for zoledronic acid was set at €80 per intravenous infusion, which reflects the day-case treatment cost according to the most recent tariffs [22]. This cost includes all hospital administration and monitoring charges as well as additional costs such as personnel costs for nurse, doctor, etc, and the cost of creatinine clearance. The administration cost of denosumab included only the cost of a healthcare professional visit, which was set at €10 based on the latest Government Gazette Issue [23]. Moreover, the reimbursement costs associated with pathological fracture, surgery to bone, and spinal cord compression were obtained from the corresponding diagnosis related groups (DRGs) tariffs issued recently by the Greek Ministry of Health [22]. In particular, the following DRGs were used in the model: pathological fracture, €2,942 (DRG code, M79M); surgery to bone, €7,063 (M09Ma); and spinal cord compression, €5,442

Table 2.
QALY decrements associated with SREs [19].

Cancer type	Pathological fracture	Radiation to bone	Surgery to bone	Spinal cord compression	Composite (weighted average) QALY loss / SRE
Breast cancer	0.045	0.092	0.130	0.113	0.064
Prostate cancer	0.052	0.097	0.076	0.088	0.080
Other solid tumors	0.041	0.070	0.036	0.108	0.060

SRE, skeletal-related event; QALY, quality-adjusted life year.

(N03M). For outpatient radiation to bone, a cost of €365 was calculated as per the relative Government Gazette Issue (290€ [radiotherapy planning] + 15 [radiotherapy sessions] * 5€ [cost/session]) [23].

Outcomes and sensitivity analysis

The primary outcome in our analysis was incremental cost-effectiveness ratio (ICER) including total cost per quality-adjusted life year (QALY) gained and per SRE avoided. A €40,000/QALY threshold is the commonly used standard, whereas a €60,000/QALY threshold corresponds to three times the per capita gross domestic product (GDP) in Greece, as recommended by the World Health Organization [24, 25]. In the context of the current economic crisis, a much lower threshold of €30,000/QALY was considered.

One-way sensitivity analyses were conducted to test the impact of denosumab cost on the primary outcome, and determine the minimum hospital price of denosumab at which this therapy could become a potential cost-effective alternative relative to zoledronic acid at the willingness-to-pay threshold of €30,000 for all tumor types.

RESULTS

Scenario 1: Denosumab is obtained and reimbursed as a hospital-administered therapy

The results of the base-case analysis where denosumab is obtained and reimbursed as a hospital-administered therapy by the pharmacy departments of the EOPYY are presented in Table 3.

Although denosumab is more effective than zoledronic acid, it is also a more expensive option. Drug acquisition accounted for 62%, 65%, and 52% of the total treatment cost in breast cancer, prostate cancer, and other solid tumors, respectively. The corresponding percentages for zoledronic acid were 56%, 57%, and 46%, respectively. Denosumab resulted in an incremental cost per QALY of €56,818 (breast cancer), €61,296 (prostate cancer), and €80,830 (other solid tumors), indicating that denosumab cannot be considered a cost-effective alternative for the prevention of SREs at a threshold of €30,000. Despite offering less cumulative SREs compared with zoledronic acid, denosumab was unable to achieve a favorable ICER of €30,000 or less. Costs per SRE avoided in relation to zoledronic acid were €3,614 (breast cancer), €4,889 (prostate cancer), and €4,854 (other solid tumors).

Scenario 2: Denosumab is assumed to be obtained from community pharmacists for subsequent injections except for the first one

In this scenario, the ICERs were €136,752 (breast cancer), €112,414 (prostate cancer), and €163,993 (other solid tumors). Additional costs per SRE avoided in relation to zoledronic acid were €8,699 (breast cancer), €8,966 (prostate cancer), and €9,847 (other solid tumors).

Scenario 3: Zoledronic acid is available at generic prices following patent expiration in 2013

When a generic price was applied for zoledronic acid, an ICER per QALY for denosumab over zoledronic was €279,114 (breast cancer), €198,431 (prostate cancer), and €328,364 (other solid tumors). In this scenario, costs per SRE avoided in relation to zoledronic acid increased to €17,755 (breast cancer), €15,827 (prostate cancer), and €19,717 (other solid tumors) (Table 4). Similar to the findings in the previous scenarios, denosumab was not found to be cost-effective at a threshold of €30,000, as drug-acquisition costs remained considerably high with respect to zoledronic acid.

Sensitivity analysis

The one-way sensitivity analysis revealed that in scenario 1 (the first injection of denosumab is delivered in a hospital and the remaining injections are delivered on an ambulatory basis), denosumab becomes cost-effective at the hospital price of €290 for breast cancer and €280 for prostate cancer and other solid tumors, when the drug is obtained from EOPYY pharmacies.

DISCUSSION

Cost-effectiveness analyses are being increasingly applied by decision-makers in an effort to quantify and compare the value of outcomes and evaluate the financial value of different treatments from the payer's perspective. In the present study, we employed cost-effectiveness analysis to determine the value for money of denosumab for Greek patients with bone metastases secondary to advanced solid tumors. According to the economic analysis, when denosumab is more effective (ie, higher QALY) and less costly than zoledronic acid, it is considered the "dominant" treatment. When denosumab is less effective and more costly, it is considered a "dominated" treatment. When denosumab is associated with higher QALY and higher cost, it is considered "cost-effective" only when the ICER is lower than a specific predetermined threshold (€30,000/QALY).

The findings of our analysis indicate that, although denosumab was more efficacious, it is associated with high drug acquisition costs and therefore, is not a cost-effective alternative to zoledronic acid (based on the established willingness-to-pay threshold of €30,000 per QALY gained). In the base-case scenario, denosumab reported an incremental cost per QALY of €56,818 (breast cancer), €61,296 (prostate cancer), and €80,830 (other solid tumor), and was unable to achieve a favorable ICER of €30,000 or less as compared to zoledronic acid. These findings are consistent across all tumor types and treatment scenarios. It must be noted that in Greece, thus far, no normative cost-effectiveness threshold exists. In the literature, different thresholds for cost-effectiveness are used, and are considered to be country-dependent (UK NICE recommends a threshold of £20,000-30,000 per QALY gained) [26].

Table 3.

Results of base-case scenario as concerns the acquisition and reimbursement of denosumab.

	Breast cancer			Prostate cancer			Other solid tumors		
	Denosumab	**Zoledronic acid**	**Difference**	**Denosumab**	**Zoledronic acid**	**Difference**	**Denosumab**	**Zoledronic acid**	**Difference**
Total SRE cost (€)	4,660	5,130	-470	2,720	2,997	-277	2,939	3,095	-156
Total drug cost (€)	7,593	6,415	1,178	5,050	4,000	1,050	3,139	2,615	525
Total cost (€)	**12,254**	**11,545**	**708**	**7,770**	**6,997**	**772**	**6,079**	**5,710**	**369**
Total QALY lost due to SRE*	-0.124	-0.136	0.012	-0.124	-0.136	0.013	-0.086	-0.091	0.005
Cost per QALY gained (€)			**56,818**			**61,296**			**80,830**
Cost per SRE avoided (€)			**3,614**			**4,889**			**4,854**

**First injection of denosumab is delivered at the outpatient hospital department and the remaining injections are delivered by a healthcare professional on an ambulatory basis (denosumab is obtained from EOPYY pharmacy departments). The horizon of this analysis is on average 22.5 months for breast cancer, 14.5 months for prostate cancer, and 9 months for other solid tumors. SRE, skeletal-related event; QALY, quality-adjusted life year.*

Table 4.

Results for scenario 3 - applying generic price for zoledronic acid.

	Breast cancer			Prostate			Other solid tumors		
	Denosumab	**Zoledronic acid**	**Difference**	**Denosumab**	**Zoledronic acid**	**Difference**	**Denosumab**	**Zoledronic acid**	**Difference**
Total SRE cost (€)	4,660	5,130	-470	2,720	2,997	-277	2,939	3,095	-156
Total drug cost (€)	7,593	3,643	3,950	5,050	2,272	2,778	3,139	1,485	1,654
Total cost (€)	**12,254**	**8,774**	**3,480**	**7,770**	**5,269**	**2,501**	**6,079**	**4,580**	**1,498**
Total QALY lost due to SRE*	-0.1236	-0.1361	0.0125	-0.1236	-0.1362	0.0126	-0.0860	-0.0906	0.0046
Cost per QALY gained (€)			**279,114**			**198,431**			**328,364**
Cost per SRE avoided (€)			**17,755**			**15,827**			**19,717**

SRE, skeletal-related event; QALY, quality-adjusted life year.

Other studies have assessed the cost-effectiveness of denosumab compared to zoledronic acid in the prevention of SREs in solid tumor patients with bone metastases using registration trial data; the majority of these studies provide robust findings that may translate to the Greek setting [27-30]. Economic studies by Xie *et al.* have shown that denosumab is not a cost-effective treatment option compared to zoledronic acid for patients with breast and hormone-refractory prostate cancers because of its high cost [27, 28]. The base-case scenario of the breast cancer study provided an incremental cost per SRE avoided amounting to €86,695 [27]. The hormone-refractory prostate cancer study reported an ICER of €53,720, which was cost-effective only for 0.3% of total cases at the threshold of €30,000 [28]. Further, Snedecor *et al.* reported that the use of denosumab in patients with breast cancer was also associated with a higher ICER compared with zoledronic acid (€527,530) [29]. Snedecor *et al.*, in a recent analysis for the patients with castration-resistant prostate cancer (CRPC), estimated a cost per QALY of €800,742 (base-case scenario), raising questions regarding the careful considerations of pharmacoeconomic values for the use of denosumab in CRPC [30].

In contrast, Stopeck *et al.* have considered denosumab as a cost-effective treatment option in the prevention of SREs in patients with CRPC, breast cancer, and non-small-cell lung cancer (NSCLC) from a US managed care perspective [31]. It is apparent that this finding does not necessarily reflect the local perspective of Greek payers, as the model was intended to evaluate the circumstances considering local budgets and economic trends from the US payer's perspective. Also, the SREs and drug administration QALY decrements reported in this study were based on time trade-off rather than EQ-5D data from the phase III clinical trials. Nevertheless, the costs per QALY gained for denosumab compared to zoledronic acid in this study for CRPC (€37,366), breast cancer (€59,685), and NSCLC (€51,377) remained costly at a threshold of €30,000/QALY from the Greek payer's perspective [31].

The present analysis conducted for the Greek setting has considered the above findings and made the best possible attempt to adhere to the standard recommendations for economic modeling. However, the model cannot substitute "real-life" direct comparisons among the alternative treatments. Hence, post-launch observational studies are needed to verify the conclusions obtained from analyses such as the one presented in this paper. Moreover, another limitation of the present analysis was that we assumed that the clinical outcomes obtained from the clinical trials and model assumptions used by Lothgren *et al.* were applicable to the Greek healthcare setting. However, in the absence of studies comparing denosumab and zoledronic acid for the prevention of SREs in the Greek population, the methodology followed in the present study was the most transparent way to perform a localized cost-effectiveness analysis. Finally, it should be noted that the results of this analysis are strictly applicable to the Greek setting and are derived on the basis of the present time resource and drug prices. Among all inputs, the model results were more sensitive to drug costs. If any of the underlying parameters change, so may the results and conclusions of this analysis.

Despite the above limitations, it should be mentioned that conducting a cost-effectiveness analysis is an important element of innovation that may be used by decision-making bodies to reward treatments that provide value for money at both at the micro- and macro-economic levels.

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Conflict of interest statement

John Yfantopoulos: Novartis, research funding; Magda Chatzikou: Novartis Hellas, employment; Peter Fishman: Novartis Pharmaceuticals Corporation, employment (until May 9, 2013); Athanasios Chatzaras and Athina Christopoulou: declared no conflict of interest.

REFERENCES

1. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. Cancer Treat Rev 2001; 27(3):165-76.
2. Coleman RE. Clinical features of metastatic bone disease and risk of skeletal morbidity. Clin Cancer Res 2006; 12(20 Pt 2):6243s-9s.
3. Coleman RE. Bisphosphonates: clinical experience. Oncologist 2004; 9(Suppl 4):14-27.
4. Coleman RE. Skeletal complications of malignancy. Cancer 1997; 80(8 Suppl):1588-94.
5. Jensen AO, Jacobsen JB, Norgaard M, Yong M, Fryzek JP, Sorensen HT. Incidence of bone metastases and skeletal-related events in breast cancer patients: a population-based cohort study in Denmark. BMC Cancer 2011; 11:29.
6. Rove KO, Crawford ED. Metastatic cancer in solid tumors and clinical outcome: skeletal-related events. Oncology 2009; 23(14 Suppl 5):21-7.
7. Lipton A. Bone metastases in breast cancer. In: Business Briefing: North American Pharmacotherapy 2005, ed. Boulton E. 2005, Stones the Printers Ltd., 109-17.
8. Hillner BE, Ingle JN, Chlebowski RT, Gralow J, Yee GC, Janjan NA, et al. American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. J Clin Oncol 2003; 21(21):4042-57.
9. European Medicines Agency. Zometa Summary of product characterstics. [modified 2012 Jun 27]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000336/human_med_001182.jsp&mid=WC0b01ac058001d124 [Accessed on March 15, 2013].
10. Miller PD. Denosumab: anti-RANKL antibody. Curr Osteoporos Rep 2009; 7(1):18-22.
11. Stopeck AT, Lipton A, Body JJ, Steger GG, Tonkin K, de Boer RH, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. J Clin Oncol 2010; 28(35):5132-9.
12. Fizazi K, Carducci M, Smith M, Damiao R, Brown J, Karsh L, et al. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a randomised, double-blind study. Lancet 2011; 377(9768):813-22.
13. Henry DH, Costa L, Goldwasser F, Hirsh V, Hungria V, Prausova J, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011; 29(9):1125-32.
14. European Medicines Agency. Xgeva Summary of product characterstics. [modified 2012 Sep 11]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002173/human_med_001463.jsp&mid=WC0b01ac058001d124 [Accessed on March 15, 2013].
15. Busse R, van Ginneken E, and Normand C. Re-examining the cost pressures on health systems. In: Figueras J and McKee M, editors. Health Systems, Health, Wealth and Societal Well-being - Assessing the case for investing in health systems. England: Open University Press; 2012. p. 37-56.
16. Government Gazette. 2912/30.10.2012. Available from: http://www.et.gr/idocs-nph/search/pdfViewerForm.html?args=5C7QrtC22wEbA_BZxkczbHdtvSoClrL8dd-Fiw3vIGbnMRVjyfnPUeJInJ48_97uHrMts-zFzeyCiBSQOpYnTy36MacmUFCx2ppFvBej56Mmc8Qdb8ZfRJqZnsIAdk8Lv_e6czmhEembNmZCMxLMtZhCZEMqd3MmByUanvyQHP9mpZRcmjwVFW78l_JNNGRM [Accessed on July 5, 2013].

17. Briggs A, Claxton K, Sculpher M. Decision modelling for health economic evaluation. In: Handbooks in health economic evaluation, ed. Gray A. and Briggs A. 2006, New York: Oxford University Press Inc., 217-25.

18. West H. Denosumab for prevention of skeletal-related events in patients with bone metastases from solid tumors: incremental benefit, debatable value. J Clin Oncol 2011; 29(9):1095-8.

19. Lothgren M, Bracco A, Lucius B, Northridge K, Halperin M, Macarios D, et al. PCN116 cost-effectiveness of denosumab versus zoledronic acid (ZA) for the prevention of skeletal-related events (sre) in patients with bone metastases from solid tumors in the Netherlands. Value Health 2011; 14(7):A455.

20. Greek Ministry of Health. Drug Pricing. Available from: http://www.yyka.gov.gr/ [Accessed on March 15, 2013].

21. Greek Ministry of Health. Drug price bulletin. Available from: http://www.moh.gov.gr/articles/times-farmakwn/deltia-timwn/1150-deltia-timwn-farmakwn-06-04-2012 [Accessed on March 15, 2013].

22. Greek Ministry of Health. Diagnostic related groups. Available from: http://www.et.gr/idocs-nph/search/pdfViewerForm.html?args=5C7QrtC22wEbA_BZxkczbHdtvSoClrL8jAxhWxkwjzrtIl9LGdkF53UIxsx942CdyqxSQYNuqAGCF0IfB9HI6qSYtMQEkEHLwnFqmgJSA5WIsIuV-nRw01oKqSe4BlOTSpEWYhszF8P8UqWb_zFijHp6ZUdAD2zK8BffwSiRGse7NJRv-IdJMsOrEbl5Pjao [Accessed on March 15, 2013].

23. Government Gazette. L.4047/2012 article 6 [Accessed on March 15, 2013].

24. Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Economics 2004; 13(5):437-52.

25. Eichler HG, Kong S, Kong SX, Gerth WC, Mavros P, Jönsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004; 7(5):518-28.

26. NICE, Measuring effectiveness and cost effectiveness: the QALY. [modified 2010 Apr 20]. Available from: http://www.nice.org.uk/newsroom/features/measuringeffectivenessandcosteffectivenesstheqaly.jsp [Accessed on March 15, 2013].

27. Xie J, Diener M, Sorg R, Wu EQ, Namjoshi M. Cost-effectiveness of denosumab compared with zoledronic acid in patients with breast cancer and bone metastases. Clin Breast Cancer 2012; 12(4):247-58.

28. Xie J, Namjoshi M, Wu EQ, Parikh K, Diener M, Yu AP, et al. Economic evaluation of denosumab compared with zoledronic acid in hormone-refractory prostate cancer patients with bone metastases. J Manag Care Pharm 2011; 17(8):621-43.

29. Snedecor SJ, Carter JA, Kaura S, Botteman MF. Cost-effectiveness of denosumab versus zoledronic acid in the management of skeletal metastases secondary to breast cancer. Clin Ther 2012; 34(6):1334-49.

30. Snedecor SJ, Carter JA, Kaura S, Botteman MF. Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: a cost-effectiveness analysis. J Med Econ 2013; 16(1):19-29.

31. Stopeck A, Rader M, Henry D, Danese M, Halperin M, Cong Z, et al. Cost-effectiveness of denosumab vs zoledronic acid for prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. J Med Econ 2012; 15(4):712-23.

NETs: Diagnostic challenge and therapeutic opportunity

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ABSTRACT

Neuroendocrine tumors (NETs) comprise a group of relatively rare neoplasms with very complex and heterogeneous clinical behavior. The incidence of these tumors according to recent epidemiological studies has been remarkably increased worldwide. This is not only due to increasing detection using new improved imaging techniques but it also seems to reflect the increase of knowledge and awareness in dealing with this real diagnostic challenge. Given their diverse biological behavior and therapeutic approaches, a proper classification of NETs is warranted. Recently, two new molecularly targeted agents, sunitinib that targets the vascular endothelial growth factor (VEGF) pathway, and everolimus that targets the mammalian target of rapamycin (mTOR) pathway, have been approved for the treatment of pancreatic neuroendocrine tumors. Here, we will review the major advances in diagnosis, classification and treatment of NETs.

Key words: neuroendocrine tumor; classification; diagnosis; treatment; targeted; sunitinib; everolimus; somatostatin.

Neuroendocrine cells (highly specialized cells with both neural and endocrine characteristics) are located in different organs such as the digestive and respiratory tracts, thymus, skin, ovaries as well as in endocrine glands such as the adrenals, pancreas, thyroid, parathyroids, and pituitary. Although their relative percentage within the gastrointestinal epithelium is only 1%, the neuroendocrine cells of the digestive tract form the major endocrine organ of the human organism. Furthermore, they are more concentrated at certain sites such as the gastric fundus-corpus, the proximal duodenum, the papilla of Vater, the terminal ileum, the appendix, the lower rectum and the pancreas. These cells receive neuronal signals-neurotransmitters and respond by releasing different molecules-hormones in the blood for regulatory purposes. This diffuse neuroendocrine cell system is responsible for the integration between the nervous and the endocrine system, a process known as neuroendocrine integration [1].

Although relatively uncommon, as compared with other tumors, the incidence of NETs appears to be rising. Based on an analysis of data from the Surveillance Epidemiology and End Results database, Yao and his colleagues estimated the incidence of NETs in the USA to be 5.25 cases per 100,000 population in 2004, an increase from 1.04 per 100,000 in 1973 [2]. This increase may in part be due to improved diagnostic skills and improvements in classification of these tumors. Whether changes in dietary habits, environmental factors, and use of certain medications such as proton pump inhibitors resulted in increased reported incidence of NETs of various types is unknown [2].

Neuroendocrine gastrointestinal tumors have classically been divided into carcinoid tumors and endocrine pancreatic tumors. Despite great behavioral differences between the two, they are grouped together as gastroenteropancreatic neuroendocrine tumors (GEP-NETs) because of cell structure similarities [3]. In the past, NETs of the ileum and the appendix were the most common GEP-NETs but recent studies revealed that probably gastric, small bowel and rectum NETs are more frequent. Apart from GEP-NETs and NETs of lungs, more rare entities are the thymus NETs, the myeloid thyroid cancer and the pheochromocytomas. Locations such as the esophagus, gallbladder, biliary ducts, liver, genital tract and skin are very rare so that it is uncertain whether they comprise primary tumors or metastases of occult or clinical undetectable primaries [4]. Almost 10% of NETs are of unknown primary

site. They usually present with liver metastases, they are mainly well-differentiated and most of them finally represent GEP-NETs. The majority of NETs are sporadic, but can be a component of a familial genetic syndrome such as multiple endocrine neoplasia (MEN) 1 and 2, Von Hippel-Lindau (VHL) disease and neurofibromatosis (NF) type 1. When there is evidence of such a syndrome (family history, multiple NETs) patients should be considered for germline DNA testing following genetic counseling. The mean age of onset is the fifth-sixth decade with the exception of the appendiceal carcinoids and the NETs in familial syndromes where the appearance is 15-20 years earlier [1, 5].

NETs have the ability to synthesize, store and secrete a variety of peptides and neuroamines, which can lead to the development of distinct clinical syndromes by the so-called 'functioning' tumors (F-NETs). However, most NETs produce but do not secrete at least sufficient amounts of biologically active substances and these 'non-functioning' tumors (NF-NETs) are diagnosed relatively late due to symptoms of mass effects and distant metastases and thus they have worse prognosis. Even in the case of functioning tumors individual symptoms can be mild or may not be evident at the time of assessment. Moreover, in most cases of gastrointestinal (GI)-NETs, serotonin (5HT), tachykinins, kallikrein, prostaglandins and other bioactive molecules can reach the systemic circulation and cause the clinical syndrome known as carcinoid only late in the course of the disease. In contrast, bronchopulmonary and ovarian NETs are associated with early manifestations due to the direct disposure of the bioactive molecules to the systemic circulation, bypassing the liver. Functioning GEP-NETs are named by the secreting hormone which is also responsible for the clinical syndrome. Therefore, they are called insulinomas, glucagonomas, gastrinomas, serotoninomas and somatostatinomas. In addition, they can produce ectopic hormones, such as vasoactive intestinal polypeptide (VIP), ACTH or GH-releasing factor.

Carcinoid syndrome includes flushing, diarrhea, cardiac fibrosis and bronchospasm. Lung and thymic NETs can cause Cushing's syndrome or acromegaly. Gastrin secretion can lead to Zollinger-Ellison syndrome (peptic ulceration, diarrhea, abdominal pain). Somatostatinomas are associated with glucose intolerance, gallstones and steatorrhea. VIPomas are characterized by watery diarrhea, hypokalemia and achlorhydria. Insulinomas lead to hypoglycemic crisis, while glucagonomas to glucose intolerance and migratory necrolytic erythema [6, 7].

Therefore, NETs present clinically in a very heterogeneous way depending on site of origin, the presence and sites of metastasis, the existence of a hereditary syndrome, tumor functionality and the type of hormone that they produce. However, a large proportion of NETs is discovered incidentally in the framework of routine examinations or on the occasion of monitoring a coexisting disease.

In this review we will focus mostly on the diagnosis, classification and recent treatment developments of gastroenteropancreatic neuroendocrine tumors.

IMMUNOHISTOLOGICAL CRITERIA

Immunohistochemically neuroendocrine cells are characterized by a strong and diffuse expression of neuroendocrine markers such as synaptophysin and chromogranin A (CgA). CD56 has recently proven to be less specific. In contrast to synaptophysin, CgA is inhomogeneously expressed in the cytoplasm of tumor cells but it can also be lacking, since its expression depends on the number of neurosecretory granules in the cell and on the cell type. In small cell NE carcinoma of the lung, generally in all the poorly differentiated NETs (due to low density of secretory granules) and in rectal NETs (due to specific cell origin) CgA is usually absent. Some tumors, as mentioned above, may also be immunohistochemically positive in specific peptide hormones or bioamines such as insulin, glucagon, somatostatin, VIP, serotonin, gastrin but they do not produce the respective syndromes. Thus, immunohistochemical staining is not the only criterion for definitive tumor classification. For example, if a tumor stains for gastrin but does not produce symptoms of the Zollinger-Ellison syndrome, it should not be considered a gastrinoma but rather a gastrin-secreting NET. Immunostaining for these hormones is optional for the diagnosis of NETs, but it can help find the primary tumor site if performed in a liver or lymph node biopsy. For example, serotonin positivity suggests a primary in the ileum; gastrin a primary in the duodenum or the pancreas; and PP/glucagon in the pancreas. Other markers are TTF-1 for lung primary, CDX2 for intestinal or pancreatic origin, PDX1 or Isl1 for pancreatic primaries and S-100 for gangliocytic paragangliomas. Several other newer markers have been reported to have prognostic value in NETs. CK19 (cytokeratin-19) is a marker of pancreatic ductal epithelium but also transiently expressed in islet cells. Its expression has been shown to correlate with worse survival in pancreatic NETs. Poorly differentiated neoplasms have more limited expression of these neuroendocrine markers and they lose their resemblance with the cells of origin [8, 9]. Following diagnosis of the neuroendocrine nature of the tumor, the differentiation and proliferation profiles have to be determined. Since early disease can be cured by surgery alone and since most NETs are already advanced when diagnosed, the right classification is crucial as it implies the therapeutic strategy.

NET CLASSIFICATION AND STAGING

Previous classification and nomenclature of NETs was complex and confusing, in part because it was specific of the organ where the tumor arises. Site-specific proposals differed in terminology and in the criteria for histological grading and staging, resulting in morphologically similar neoplasms being classified differently based on the site of origin. Stage and grade are the main prognostic factors of

NETs but until recently there was not one single system of nomenclature [7]. However, features such as tumor proliferative rate and local extent are now generally similar. The latest World Health Organization (WHO) classification of 2010 has adopted the staging system proposed by the European Neuroendocrine Tumor Society (ENETS), which is similar to most other non-neuroendocrine epithelial neoplasms, and a grading system applicable to most of these tumors [7, 9-10] (Table 1). This ENETS grading proposal was adopted also by the AJCC but the staging proposal was modified, without clear evidence of which one better separates prognostically the different groups. NETs are generally classified according to the site of origin and histology. The classification for bronchial and thymic neuroendocrine tumors is presented in Tables 2 and 3.

According to the ENETS grading scheme, pure NETs are separated in well-differentiated (subdivided to low-G1 and intermediate-G2 grade) and poorly differentiated which are all high-G3 grade and are named neuroendocrine carcinomas (NECs). The latter are subdivided into small- and large-cell carcinomas. When there is a non-endocrine component, usually adeno- or squamous cell carcinoma, these neoplasms are called mixed neuroendocrine carcinomas and mainly behave like carcinomas without endocrine component and must be distinguished from the pure NETs [9, 10]. In general, the well-differentiated NETs are much more

Table 1.
Histological classification of neuroendocrine tumors.

Differentiation	Grade	Mitotic count	Ki-67 index (%)	ENETS/WHO
Well-differentiated	Low grade (G1)	<2 per 10 HPF	≤2	Neuroendocrine tumor, grade 1 (G1)
	Intermediate grade (G2)	2-20 per HPF	3-20	Neuroendocrine tumor, grade 2 (G2)
Poorly differentiated	High grade (G3)	>20 per HPF	>20	Neuroendocrine carcinoma, grade 3 (G3), small cell
				Neuroendocrine carcinoma, grade 3 (G3), large cell

ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high-power fields.

Table 2.
Histological classification of bronchial neuroendocrine tumors.

Differentiation	Grade	Mitotic count (per 10 HPF)	Necrosis	ENETS/WHO
Well-differentiated	Low grade (G1)	<2	AND Absent	Typical carcinoid (TC)
	Intermediate grade (G2)	2-9	OR Present (focal)	Atypical carcinoid (AC)
Poorly differentiated	High grade (G3)	>9	OR Present (extensive)	Large cell neuroendocrine carcinoma (LCNEC)
		>50	OR Present (extensive)	Small cell neuroendocrine carcinoma (SCNEC)

ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high-power fields.

Table 3.
Histological classification of thymic neuroendocrine tumors.

Differentiation	Grade	Mitotic count (per 10 HPF)	ENETS/WHO
Well-differentiated	Low grade (G1)	<10	Typical carcinoid (TC)
	Intermediate grade (G2)	10-20	Atypical carcinoid (AC)
Poorly differentiated	High grade (G3)	>20	Large cell neuroendocrine carcinoma (LCNEC)
			Small cell neuroendocrine carcinoma (SCNEC)

ENETS, European Neuroendocrine Tumor Society; WHO, World Health Organization; HPF, high-power fields.

common (by a rate of 10:0.5) than the poorly differentiated NECs. However, at certain locations such as the esophagus, the colon or the lungs the poorly differentiated NECs are more frequent than their well-differentiated counterparts.

Neuroendocrine tumor grading by the ENETS/WHO system is based on proliferative rate, measured by mitotic activity and/or the Ki67 labeling index [9, 10]. According to the WHO guidelines, mitotic activity is measured on 40 to 50 high power fields (HPF) and is reported as the number of mitoses per 10 HPF or per 2mm^2. However, it may not be possible to calculate the mitotic rate when the amount of tumor tissue is inadequate. The Ki67 index should be assessed in 2000 cells and is reported as the percentage (%) of the neoplastic cells labeling for this proliferation marker. If there is intratumoral disparity, the regions with the highest rates ("hot spots") of the mitotic rate and Ki67 index should be counted and the higher grade should be assigned [11]. Mitotic activity can be assessed only in large enough biopsy specimens or after surgery, and there is no general agreement as to the cutoff values that best separate different grades, especially among NETs of different origin. For example, the cutoff of poorly differentiated GEP NETs is 20/10 HPF but for bronchial NETs it is 10/10. Even though there is no quality difference in grading assessment between mitotic counting and Ki67 labeling, the latter offers several advantages but when there is sufficient tumor, accurate mitotic counting is preferred. Also the WHO classification of lung and thymus tumors relies only on mitotic rate, but for GEP-NETs mitotic rate and Ki67 are equally used. In case of discordance between these two methods, the WHO recommends using the higher grade.

Well-differentiated NETs include tumors that were traditionally referred to as carcinoid (G1) and atypical carcinoid (G2). The term carcinoid tumor remains in use, both in the official WHO classification of NETs of the lung and thymus and even though it is not in the official terminology for NETs of other sites, it still remains a synonym of widespread usage [9]. These well-differentiated tumors may have similar histological characteristics but are different in pathogenesis and biological behavior. They generally have an indolent course and good prognosis with an overall five-year survival of 67% but, as NETs of the digestive tract represent a very heterogeneous group, they can have a varying spectrum of aggressiveness. Despite their slow-growing pattern, more than 40% will have already metastasized by the time of diagnosis, mainly to the liver. This is the reason why the term carcinoid has been criticized, as it does not describe the potential malignant behavior. In contrast, poorly differentiated NECs comprise highly proliferative cells, are frequently very aggressive and follow a rapid clinical course.

TUMOR MARKERS

All substances produced by neuroendocrine cells can serve as tumor markers that may also have, apart from their diagnostic and monitoring role, a prognostic one as well [12, 13]. Chromogranins (Cg) A and B are glycoproteins found in NE cells. NETs usually have increased plasma levels of CgA and less frequently of CgB. Assays measuring the whole CgA molecule have higher sensitivity than those who define parts of it and should be preferred and followed in all serial measurements. Interpreting the results must be performed cautiously, since other conditions such as renal failure, chronic atrophic gastritis or proton pump inhibitors can increase CgA. CgB, if expressed, is not affected by any of these situations but there is no commercial assay for CgB available yet. Tumor burden and biological activity correlate with the CgA levels and has been shown to be an independent prognostic factor for small well-differentiated intestinal NETs [14]. Moreover, CgA has some role in monitoring and early diagnosis of a tumor relapse [15]. Pancreatic polypeptide (PP), produced by PP cells located in the gut and pancreas, is elevated in NETs of this origin but it has the same limitation of low specificity as CgB. In NF-NETs measurement of CgA and PP may be useful, as it has a sensitivity of 95%. Neuron-specific enolase (NSE) is another tumor marker with less specificity than CgA, most frequently elevated in small-cell lung cancer patients and in 40% of GEP-NETs, medullary thyroid cancer and in pheochromocytomas. From the urinary markers, the most useful one is 5-hydroxyindolacetic acid (5-HIAA), a metabolite of serotonin, in carcinoid tumors. Its levels depend on tumor volume but they can also be affected by a variety of drugs and the ingestion of certain foods. Lately, N-terminal pro-brain natriuretic peptide (NT-pro-BNP) has been proven to be an excellent biomarker of carcinoid heart disease also exerting a high negative predictive value [16]. In general, CgA is the most important tumor marker, not specific for a particular NET type, and should be measured in every patient with a suspected NET [13]. PP can help distinguish pancreatic NETs (pNETs) and other GEP-NETs. NSE may be of value particularly in poorly differentiated NET and all other specific markers are tested only when the clinical presentation predicates it. Given the delay of 5-6 years in diagnosis of metastatic NETs the identification of more sensitive markers that will help the early detection of the disease is warranted; currently, no such tumor marker exists. In one study circulating mRNA from GI NETs proved sensitive enough, whereas circulating plasma Tryptophan hydroxylase 1 (Tph-1) exerted a specificity of 100% [17]. The combination of circulating 5-hydroxytryptamine (5-HT), CgA, ghrelin, and connective tissue growth factor (CTGF) fragments in a formulated algorithm increased the sensitivity of detecting GI NETs to 82% [17]. Lately, circulating tumor cells are utilized as a means of further increasing sensitivity.

IMAGING TOOLS

The diagnosis of NETs has been facilitated by the development of several imaging techniques over the last decades. The choice of imaging methods is based on tumor location.

The aim is to guide needle biopsies in order to obtain a tumor tissue specimen; to evaluate disease stage, tumor somatostatin receptor expression and response to therapy; and early detection of relapse. Lung, gastric, duodenal, rectal and colonic NETs are basically diagnosed by endoscopy, but for other primaries specific imaging methods must be used [18, 19].

Ultrasonography (U/S) is an operator-dependant examination leading to a wide variety of sensitivity and specificity in the literature. Contrast-enhanced US (CEUS), endoscopic ultrasonography (EUS) and intraoperative US (IOUS) are the main modalities in use and have been shown to be more sensitive than conventional U/S in detecting mainly pancreatic NETs, liver metastases and rectal NETs.

Computed tomography (spiral or helical) is widely available with a mean sensitivity of 95% and specificity of 73% for diagnosing pNETs, NETs in the abdomen and thorax and distant metastases. However, it is not the examination of choice for small bowel NETs, where a CT enteroclysis may be needed [20].

Magnetic resonance imaging (MRI) has a mean sensitivity of 93% and specificity of 88% and is the method of choice for detecting liver, bone and mesenteric metastases. MRI as well as EUS is useful for rectal NET detection and evaluation of its invasion of the rectal wall, the surrounding mesorectum and adjacent organs. High-quality MRI, including dynamic imaging with intravenous contrast, can be achieved only when it is performed in a limited part of the body, thus it is not recommended for whole body imaging. Consequently, taking also into consideration the limited availability of MRI, it is better to be used as differentiation tool in areas where there is a strong suspicion for NET but it is not documented via other imaging techniques. In general, CT and MRI imaging is important as the size of the lesions is more easily calculated according to RECIST criteria, it is more reliable and can help to monitor response to therapy, in contrast to U/S.

Nuclear medicine plays a pivotal role in the imaging of NETs [21]. Somatostatin receptor scintigraphy (SRS) commonly with ^{111}In-pentetreotide (^{111}In-Octreoscan) can detect even radiologically occult NETs but can also reveal distant metastases when there is a positive primary uptake. In addition, SRS evaluates somatostatin receptor (SSTR) status and possibly the eligibility for therapy with somatostatin analogues. SRS is based on the predominant expression of subtype 2 SSTRs from the tumor cells. SSTRs are also expressed in various normal tissues, such as the central nervous system, anterior pituitary, thyroid, pancreas, GI tract and adrenals, in different density. ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) is based on the metabolic activity of the tumor and can be useful in high-grade, poorly differentiated NECs, where SRS is usually non-diagnostic [22, 23]. Unfortunately, most GEP-NETs are well-differentiated and FDG-PET is of limited use only in cases of less differentiated tumors. Indeed, according to a recent study, it seems that there is a negative correlation between ^{18}F-FDG uptake and prognosis. The use of ^{68}Ga-labeled octreotide or octreotate (^{68}Ga-DOTA-TOC or TATE) PET is based on the use of different radiolabeled somatostatin analogues with higher affinity to SSTRs and has a sensitivity and specificity near 95% [29, 30]. Other molecular tracers, apart from somatostatin analogues that are in use in PET imaging, are ^{18}F-DOPA and ^{11}C-5-HTP. L-3,4-dihydroxyphenylalanine (L-DOPA) is a catecholamine precursor, taken up by the neuroendocrine cells and 5-hydroxy-L-tryptophan (5-HTP) is a precursor of serotonin. The first one is a good imaging tool for carcinoid tumors and the second one for pancreatic NETs [21]. All these latest PET modalities are very promising but still limited to only a few centers. Combined techniques of SRS or PET with CT or MRI are very encouraging in terms of improved imaging quality and better detection of the primary tumor and metastatic disease. Additionally, in the era of the new molecular therapies, the addition of functional modalities to morphological imaging can better reveal the therapeutic result.

MOLECULAR PATHWAYS

New insights in the complex signaling mechanisms of NET development, growth and metastasis have provided the basis for evaluating new targeted treatments for these tumors [24, 25]. Until recently, very little was known about the genetic profile of sporadic NETs. Evidence from familial syndromes revealed germ line mutations of the MEN-1 gene in 70-90% of MEN-1 families and in 95% loss of heterozygosity of the MEN-1 locus. In VHL syndrome a combination of VHL gene mutations and 3p loss of heterozygosity can lead in 15% of cases to the development of endocrine pancreatic tumors. Neurofibromatosis and tuberous sclerosis are caused by inactivation of the tumor suppressor genes such as NF-1 and TCS-1 and 2. Knowing that NF-1 regulates TCS-1 and 2 through the mammalian target of rapamycin (mTOR), loss of NF-1 function leads to mTOR activation and tumor growth [26]. Somatostatin and somatostatin receptors, belonging to the G-protein-coupled receptor family, and tyrosine kinase receptors like the insulin-like growth factor 1 receptor (IGF1R) have been shown to control cell proliferation in GEP-NETs. Vascular endothelial growth factor (VEGF) and its receptor (VEGFR), as well as platelet derived growth factor (PDGF) and its receptor (PDGFR) in endothelial cells and pericytes are crucial in promoting angiogenesis. The phosphatidylinositol 3-kinase (PI3K)-Akt and phospholipase C/protein kinase C pathways are involved in VEGFR and PDGFR downstream signaling, and the PI3 K/Akt/m-TOR, RAS/RAF/MAPK and JAK/STAT pathways for signal transduction of IGFR-1 and somatostatin receptors. Hindgut NETs express transforming growth factor α (TGF-α) and epidermal growth factor receptor (EGFR), whereas foregut NETs have frequent mutations and deletions of the MEN-1 locus [26]. The better understanding of genetic defects in sporadic NETs and in those associated with inherited syndromes will help in the development of new treatments.

THERAPY

Several treatment modalities are available for patients with NETs. Although the aim of treatment should be curative where possible, in the majority of cases it is palliative. Patients often maintain a good quality of life over a long period despite having metastases. For all patients, the aim is to keep them free from disease and symptoms for as long as possible.

Factors that influence the management of these patients include tumor type and location; histological characteristics (differentiation and proliferation index); extent of the disease (stage); symptoms from the secretion of bioactive substances; and patient's general status. Surgery, whenever possible, is the only curative treatment for NETs. Other treatments include somatostatin analogues, systemic chemotherapy, targeted therapies, liver-directed therapies and peptide receptor radionuclide therapy. A simplified treatment algorithm for advanced NETs according to the WHO classification is shown in Figure 1. Herein, we will focus on the therapeutic modalities used mostly in well- or moderately-differentiated NETs of the pancreas and gastrointestinal tract (gastroenteropancreatic NETs).

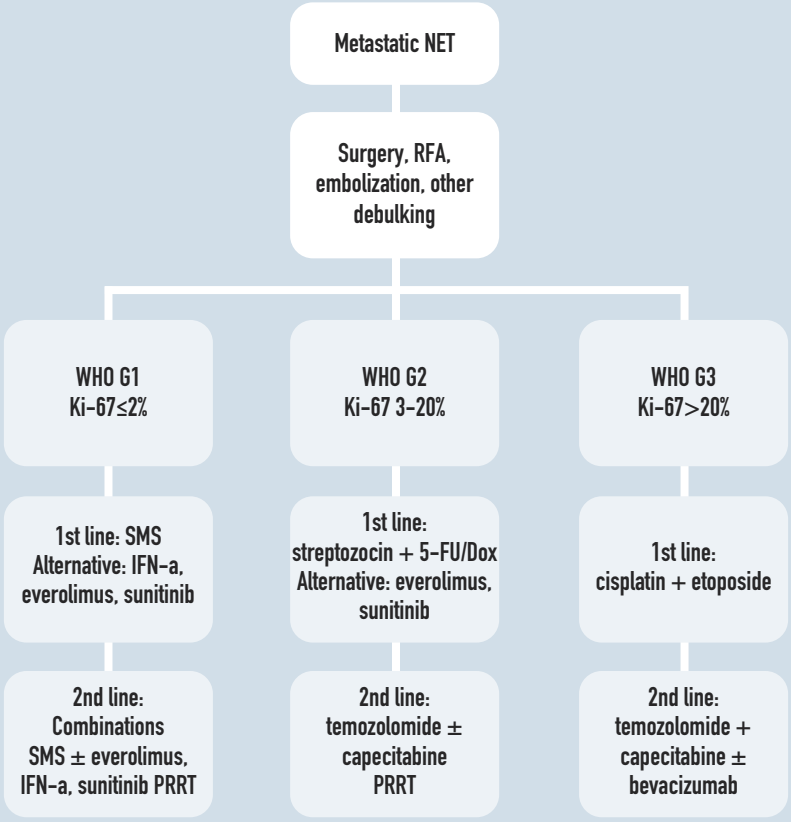
Surgery for GEP-NETs

Gastrointestinal carcinoid tumors

The treatment of choice for a patient who has a localized carcinoid tumor is usually surgery. The extent of the surgical resection depends on the site of origin and primary tumor size. Gastric carcinoids are divided into three categories that differ in biological behavior and prognosis. Type 1 is associated with chronic atrophic gastritis and elevated gastrin levels; type 2 is also characterized by elevated gastrin levels usually in association with gastrinoma (Zollinger-Ellison syndrome); while type 3 sporadic carcinoids are not associated with atrophic gastritis or Zollinger-Ellison syndrome [27]. For type 1 and 2 gastric carcinoids smaller than 1 to 2cm,

Figure 1.

Simplified treatment algorithm for advanced NETs according to WHO classification (Adapted from Oberg K, Ref. 80).



NET, neuroendocrine tumor; RFA, radiofrequency ablation; SMS, somatostatin; IFN-a, interferon-a; 5FU, 5-fluorouracil; DOX, doxorubicin; PRRT, peptide receptor targeted radiotherapy.

endoscopic resection represents adequate therapy while for tumors larger than 2cm endoscopic resection (if possible) or surgical resection is indicated. Type 3 carcinoids are more aggressive and partial or total gastrectomy with lymph node dissection is recommended [28]. Tumors of the jejunum, ileum or colon are treated with surgical resection of the bowel with regional lymphadenectomy. Appendiceal carcinoids represent a special category as tumors are often found incidentally at appendectomy and prognosis is influenced mainly by tumor size. In general, for tumors greater than 2cm or those with mesoappendiceal invasion it is recommended to perform a right hemicolectomy, while for those smaller than 1cm, simple appendectomy is adequate [29].

Pancreatic NETs (pNETs)

For localized pNETs, resection is the main modality used and can result in excellent outcomes with 5-year survival rates of 61% and 52% for stage I and II tumors, respectively [30]. There are many factors that need to be considered, including the presence of clinical symptoms, tumor size and location; tumor malignancy potential; extent of the disease; and the presence of metastases. In cases of preoperative symptoms of hormonal excess, such symptoms need to be treated, most of the times with the use of somatostatin analogues (octreotide). The type of surgery depends mostly on tumor location and may include pancreaticoduodenal resection (Whipple's resection), distal pancreatectomy or enucleation. Insulinomas are frequently benign and when peripheral and easily located during surgery, enucleation is usually sufficient. Laparoscopic resection may be performed in specialized centers [31]. Frequently, pNETs are malignant and there could be lymph node involvement even in tumors that are 1-2cm in size [32]. Therefore, lymph node dissection is required in the surgical treatment of pNETs.

Role of surgery in metastatic NETs

Metastatic liver involvement is frequently seen in GEP-NETs and liver resection can be performed in about 10% of the cases when one lobe is involved. If liver metastases are present at diagnosis, resection of the primary tumor and of the liver metastases could be considered and may be performed at the same time or as a staged procedure. Hepatic resection of metastases can improve symptoms, and may also be performed in selected cases if a significant proportion of the tumor bulk can be resected, with similar survival in patients undergoing 90% liver debulking as in those who have complete resection [33-35]. In a multi-institutional international series of 339 patients with neuroendocrine tumor and liver metastases, who were surgically managed, the 5- and 10-year survival was 74% and 51%, respectively [36]. However, disease recurred in 94% of the patients at 5 years.

Liver-directed therapies

Several techniques have been used as palliative treatments in patients with NETs and hepatic metastases. Several modalities for hepatic artery embolization have been used, including bland embolization, chemo-embolization (doxorubicin, cisplatin, streptozocin), embolization with chemotherapy eluting beads or radioisotopes [37-39]. These modalities offer mostly palliation of symptoms, benefiting 70-90% of the patients. There could also be radiological improvement of metastases but it is largely unknown whether there is any benefit in survival. Post-embolization survival rates of 28-44% have been reported in patients with NET liver metastases. However, some serious adverse events could also occur, including sepsis, hepatorenal syndrome and necrotizing cholecystitis in 7.5-23.8% of the patients. Careful patient selection is mandatory in order to avoid major complications. Embolization of the hepatic artery with 90Y microspheres has been used with evidence of some benefit. In a study of 148 patients, the symptomatic response rate 55% at 3 months and 50% at 6 months. Imaging response was stable disease in 22.7%, partial response in 60.5%, complete response in 2.7% and progressive disease in 4.9%, while the median survival was 70 months [40]. Also, ablative techniques (radiofrequency ablation, cryotherapy, microwave ablation) could be used in selected patients with palliative effect [41]. However, there are no randomized trials that have evaluated the effectiveness of these liver-directed therapies as compared to surgery or systemic treatments.

In patients with neuroendocrine tumors and liver-only metastases, liver transplantation has been attempted in a relatively small number of patients. A report from the United Network for Organ Sharing (UNOS) database on 150 liver transplants performed between 1988 and 2008 in patients with NETs, showed 1-, 3- and 5-year survival of 81%, 65% and 49%, respectively [42]. However, the majority of patients undergoing liver transplantation develop recurrent disease.

Systemic treatment of neuroendocrine tumors

The aim of systemic treatment of advanced NETs is to control symptoms due to hormone hypersecretion as well as due to tumor growth. The classification systems used differentiate between more indolent tumors which are well- or moderately-differentiated and more aggressive tumors that are poorly differentiated and most commonly treated with platinum-based chemotherapy similar to small-cell lung cancer. Systemic treatments that can be used include somatostatin analogues, systemic chemotherapy, targeted agents and targeted radiotherapy. Herein, we will focus on systemic treatments used in well- and moderately-differentiated tumors.

Somatostatin analogues

Symptom control

Frequently, patients with metastatic NETs and especially GEP-NETs, develop symptoms due to hormonal hypersecretion, rather than the tumor bulk. This is most

commonly seen with pancreatic NETs and also with midgut carcinoids in which hormonal symptoms are evident after the development of liver metastases. Somatostatin receptors (SSTRs) are present in the majority of NETs and it seems that SSTR2 and SSTR5 are the most important for hormonal secretion inhibition in functioning NETs [43]. As natural somatostatin has a very short half-life (2-3 min), analogues with longer half-lives have been developed, which bind to these receptors and inhibit the release of various hormones in the gut, pancreas and pituitary. Two somatostatin analogues (SSAs) are available: octreotide and lanreotide. Internationally, both octreotide and lanreotide are licensed for the control of NET symptoms, while lanreotide is licensed in the USA for the treatment of acromegaly. Somatostatin analogues produce both biochemical responses (in 30-70% of the patients) and also control symptoms in the majority of patients. In a pooled analysis of octreotide and lanreotide trials over the past 20 years, that included 476 patients, a mean symptomatic response rate of 73.2% was noted [43]. These agents are more effective in controlling symptoms associated with carcinoid tumors, VIPomas and glucagonomas, while their efficacy is less predictable for symptomatic insulinomas. Immediate-release octreotide has to be administered subcutaneously 2-3 times daily and symptomatic patients generally receive initial treatment with daily injections and are subsequently switched to one of the longer-acting forms. These longer-acting forms are octreotide long-acting-release (LAR), lanreotide Autogel and lanreotide LA. Standard doses of long-acting formulations is octreotide 20-30mg/4 weeks intramuscularly (with dose escalation up to 60mg/4 weeks) and lanreotide Autogel 90-120mg/4 weeks subcutaneously [43, 44]. These long-acting agents have shown improvement in the quality of life of patients with NETs, have comparable or better efficacy than short-acting octreotide and are considered the treatment of choice for symptomatic treatment of NETs; while short-acting octreotide can be used over short periods for breakthrough symptoms and for the management of carcinoid crisis [45]. Short-acting octreotide is also used prophylactically in patients with carcinoid syndrome who will undergo major surgery or hepatic artery embolization in order to avoid a carcinoid crisis.

Adverse effects of somatostatin analogues are generally mild and usually subside over time. Patients may experience local reactions at the injection site, mild nausea, abdominal discomfort and cramps, flatulence and loose stool. Also mild glucose intolerance may occur, due to temporary inhibition of insulin secretion. Additionally, there is a risk of cholelithiasis in 10-50% of the patients and it is recommended for patients who are already receiving or about to receive long-term somatostatin analogues, and undergo abdominal surgery, to have a prophylactic cholecystectomy too.

Pasireotide is a novel somatostatin analogue with higher binding affinity than octreotide for SSTR5 (40-fold), SSTR1 (30-fold) and SSTR3 (5-fold) and the same affinity for SSTR2 [46]. In a phase II study it was effective in controlling symptoms in 27% of patients with carcinoid tumors in whom treatment with octreotide LAR had failed [47]. An ongoing phase III study compares the long-acting formulations pasireotide LAR and octreotide LAR in patients with advanced NETs (NCT00690430).

Other treatments that may be required depending on the hypersecreted hormones from NETs may include proton pump inhibitors (gastrinoma), diazoxide (insulinoma), fluid and electrolyte replacement (VIPoma).

Antiproliferative effect of somatostatin analogues

The efficacy of somatostatin analogues in controlling tumor-associated symptoms has raised the possibility that these agents could also have an antitumor effect. In earlier studies it was seen that octreotide stabilized tumor growth in up to 50% of the cases [48], but there was generally poor evidence of tumor response and their usefulness as an antineoplastic treatment was controversial. In pancreatic NETs, tumor responses (partial or complete) have been reported in less than 10% of the patients, although stable disease has been noted in 24-57% of the patients, and similar results have been reported for midgut NETs [45].

The effect of octreotide LAR in controlling tumor growth in patients with metastatic neuroendocrine midgut tumors was evaluated in the PROMID study [49]. This was a randomized, placebo-controlled, prospective, double-blind study, where 85 treatment-naïve patients with advanced well-differentiated midgut neuroendocrine tumors were randomized to either placebo or octreotide LAR 30mg intramuscularly every month. The primary endpoint was time to tumor progression (TTP) and secondary endpoints were overall survival and tumor response. The results showed that median TTP in the octreotide LAR and placebo groups was 14.3 and 6 months, respectively (HR=0.34, p=.000072). At 6 months, stable disease was seen in 66.7% of the patients in the octreotide group and 37.2% in the placebo group, while there was only one partial response and no complete responses. It was observed that functionally active and inactive tumors responded similarly and the most favorable effect was seen in patients with low hepatic tumor load and resected primary tumor.

Based on these results, the use of somatostatin analogues, specifically octreotide LAR, is recommended by the ENETS guidelines for antiproliferative purposes in functioning and non-functioning midgut tumors [44]. However, the timing of treatment initiation is controversial, as it remains unclear whether early treatment is better than a "watch-and-wait" strategy until tumor progression. For well-differentiated tumors originating in the gastroduodenum or pancreas there is evidence from retrospective and non-randomized prospective studies that SSAs could be useful [50, 51]. For grade II tumors there is insufficient data for the efficacy of

somatostatin analogues but these could still be used, although alternative therapies may be considered. For metastatic neuroendocrine carcinomas (NEC) grade III, treatment with SSAs is not recommended and these patients should be treated with chemotherapy.

Interferon

Interferon alpha (IFNa) has been used for the treatment of neuroendocrine tumors (especially carcinoid) for many decades. Its antitumor effects are exerted via T-cell stimulation, cell cycle arrest and also through angiogenesis inhibition [52]. In a review of more than 500 patients reported in the literature with GEP-NETs and treated with IFN, tumor responses were generally low (11%), while subjective response rate was 60% and biochemical responses were seen in 44% of the patients [54]. The combination of IFN and SSA has been compared with SSA alone in three prospective randomized studies in patients with metastatic GEP-NETs. The results showed that there was no difference in the antiproliferative effect of the combination versus monotherapy with SSA [50, 51, 53]. However, these studies were likely underpowered to detect significant differences between the two arms. Significant side-effects due to IFN are also another reason for its limited use in the treatment of patients with NETs. Perhaps the main indication for IFN use is in patients with advanced carcinoid who have disease or symptom progression while on treatment with a somatostatin analogue.

Chemotherapy

In general, chemotherapy is recommended in advanced pancreatic NETs, metastatic foregut NETs G2, and in NEC G3 of any site.

Chemotherapy in pNET

Chemotherapy agents that have been used in pNETs include streptozocin, 5-fluorouracil, doxorubicin, and more recently oxaliplatin, irinotecan and temozolomide. Streptozocin has been the mainstay treatment in the past 30 years with single agent response rates of about 42% [55]. In a randomized study of 84 patients with advanced islet-cell carcinoma, the combination of streptozocin plus fluorouracil had advantages over streptozocin alone in overall rate of response (63 vs. 36 per cent) and in rates of complete response (33 vs. 12 per cent) [56]. In a seminal study by Moertel *et al.*, 105 patients with advanced pancreatic islet-cell tumors were randomized to receive one of three treatment regimens: streptozocin plus fluorouracil; streptozocin plus doxorubicin; or chlorozotocin alone. The combination of streptozocin and doxorubicin resulted in greater biochemical and radiological responses (69 vs. 45%, p=0.05) and longer overall survival (2.2 vs. 1.4 years, p=0.004) compared to the combination of streptozocin and 5-FU [57]. The high response rates reported in this trial were not reproduced in other studies, probably due to the non-standard response criteria used in the Moertel study. In a retrospective study of 84 patients with non-resectable pNETs treated with the combination of streptozocin, 5-FU and doxorubicin, the overall response rate was 39% and the median survival was 37 months [58].

Dacarbazine, which is an alkylating agent like streptozocin has shown activity in pNETS. In a phase II study, involving 42 patients with advanced pNETs, the response rate was 33% [59]. However the toxicity of dacarbazine-based regimens has limited its use. Temozolomide, a less toxic oral analogue of dacarbazine has shown activity in combination with capecitabine in patients with pNETs. In a retrospective study, 30 patients with pNET were treated with this combination and there was a very promising response rate of 70% [60].

Newer cytotoxic agents have been explored in small, single-agent trials, including the taxanes [61], gemcitabine [62], pemetrexed [63], and topotecan [64], but the response rates have been less than 10%.

Chemotherapy in carcinoid tumors

Contrary to pNETs, the role of chemotherapy in carcinoid tumors is not as clear. In one randomized study the combination of 5-FU/streptozocin was compared to single agent doxorubicin in 172 patients with metastatic carcinoid tumor. Response rates were 22% and 21%, respectively and there was no difference in survival [65]. In another randomized study 5-FU/doxorubicin was compared to 5-FU/streptozocin, in 176 patients, and the response rate (by WHO criteria) was 16% in both arms, but there was superior survival of 24 months with 5-FU/streptozocin vs. 16 months with 5-FU/doxorubicin (p=0.0267) [66]. Patients crossed over to dacarbazine (DTIC) treatment after disease progression following first-line treatment and the response rate of crossover DTIC treatment was only 8.2%, with a median survival of 11.9 months.

Temozolomide showed limited activity in a retrospective series that included 44 carcinoid tumor patients treated with temozolomide-based regimens; only one (2 percent) had an objective tumor response [67]. The majority of these patients had primary gastrointestinal carcinoids.

There are some reports from phase II non-randomized studies showing some activity with metronomic 5-FU in combination with octreotide, or capecitabine and oxaliplatin in well-differentiated NETs including midgut tumors but their value remains unclear [68, 69]. According to the 2012 ENETS guidelines, patients with well-differentiated metastatic midgut NETs generally should not receive current cytotoxic regimens [44]. Chemotherapy might be an option exclusively in advanced intestinal NETs after failure of previous treatment lines. Also, according to the NCCN guidelines, anticancer agents such as capecitabine, dacarbazine, 5-FU, interferon-alpha (IFNa), and temozolomide can be used in patients with progressive metastases from carcinoid when there are no

other treatment options. However, objective radiological responses are rare, and no chemotherapy drug or regimen has demonstrated a PFS or overall survival benefit.

Targeted treatments

Over the past few years there have been significant advances in understanding the molecular pathways involved in the development of NETs [70]. Several targets are expressed in neuroendocrine cells, including cellular growth factors and their receptors, like VEGF, VEGFR, PDGF, PDGFR, EGFR and others. NETs are highly vascularized tumors indicating that the activation of angiogenesis plays an important role in its pathogenesis. Studies have shown that VEGF and HIF activation markers are overexpressed in NETs and influence prognosis [71]. The mammalian target of rapamycin (mTOR) pathway regulates cell growth, metabolism, proliferation and angiogenesis and plays a role in neuroendocrine tumor growth and is frequently activated in pancreatic NETs [72], but there is also evidence for activation in carcinoid tumors as well [73]. These facts have led to the investigation of angiogenesis and mTOR inhibitors for the treatment of NETs, resulting in the approval of sunitinib and everolimus for use in these tumors. Similarly to cytotoxic chemotherapy, these agents seem to be more active in pancreatic NETs than in carcinoids. Completed randomized studies of targeted agents in NETs are presented in Table 4.

Angiogenesis inhibitors

Several agents inhibiting angiogenesis have been tried in NETs, including the anti-VEGF antibody bevacizumab and VEGFR tyrosine kinase inhibitors (sorafenib, sunitinib, pazopanib).

A. Angiogenesis inhibitors in pNETs

In pancreatic NETs, the majority of evidence comes from the use of small molecule tyrosine kinase inhibitors (TKIs). Sunitinib is a multi-kinase inhibitor with activity against multiple signaling pathways and growth factor receptors including VEGFR 1, 2 and 3, PDGFR-α and -β, Kit and others. In a phase II study, sunitinib (50mg daily for 4 of every 6 weeks) was administered to 109 patients with advanced NETs [74]. Overall objective response rate (ORR) in pancreatic endocrine tumor patients was 16.7% (11 of 66 patients), and 68% (45 of 66 patients) had stable disease (SD) while among carcinoid patients the ORR was 2.4% (one of 41 patients). Median time to tumor progression was 7.7 months in pancreatic neuroendocrine tumor patients. This led to an international placebo-controlled phase III trial of patients with progressing pNETS.

In this trial, 171 patients with well-differentiated (G1/G2) advanced pNETs progressing within 12 months were randomized to treatment with sunitinib (37.5mg continuous dose) or placebo [75]. The primary endpoint was progression-free survival; secondary endpoints included objective response rate, overall survival, and safety. The study was discontinued early, after the independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo group as well as a difference in progression-free survival favoring sunitinib. Median PFS was significantly longer with sunitinib (11.4 versus 5.5 months, HR 0.42, p<0.001). The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. The most frequent adverse events in the sunitinib group were diarrhea, nausea, vomiting, asthenia, and fatigue. Palmar-plantar erythrodysesthesia and hypertension of any grade occurred in 23% and 26% of patients receiving sunitinib, respectively. The most common grade 3 or 4 adverse events in patients who received sunitinib were neutropenia (12%) and hypertension (10%). Despite these side-effects, there were no differences in the quality of life index with sunitinib. Based on this data, sunitinib has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of advanced and progressive well-differentiated pancreatic NETs. The majority of patients in this study had received systemic therapy before and the exact position of sunitinib in

Table 4.
Completed randomized trials with targeted agents in NETs.

Author	Therapy	Tumor	No. of patients	Results
Raymond [75]	Sunitinib vs. BSC	pNET	171	PFS 11.4 vs. 5.5 months ORR 9.3 vs. 0%
Yao [85]	Everolimus vs. Placebo	pNET	410	PFS 11.0 vs. 4.6 months ORR 5% vs. 2%
Pavel [87]	Everolimus + Octreotide vs. Octreotide	NET associated with carcinoid syndrome	429	PFS 16.4 vs. 11.3 months (p=0.026, not significant as per statistical design)

BSC, best supportive care; pNET, pancreatic neuroendocrine tumor; PFS, progression-free survival; ORR, overall response rate.

the treatment algorithm of pNETS is not yet clear. There is no long-term safety data available and the response rates with systemic chemotherapy seem to be higher (30-40%). It is suggested that the main indication for sunitinib is in second- or third-line treatment [44]. There are also some limitations in this study that include premature end of the study that could not allow the estimation of overall survival and the fact that early termination may result in over-estimation of the treatment effect and prevent rigorous exploratory subanalyses [76].

Two other TKIs, sorafenib and pazopanib, have been evaluated in pNETs in phase II studies and have shown modest activity. Sorafenib, a small-molecule inhibitor of the VEGFR-2 and PDGFR-ß tyrosine kinase domains, was evaluated in a phase II study that included 50 patients with carcinoid tumors and 43 patients with pNETs. In a preliminary report a response rate of 11% was observed in patients with pNETs [77]. Pazopanib, which targets VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α and -ß, was evaluated in a prospective study of 51 patients with advanced NET who were also receiving octreotide LAR, including 29 with pancreatic NETs. The response rate among patients with pancreatic NETs was 17% [78].

B. Angiogenesis inhibitors in carcinoids

Small molecule TKIs have been evaluated in advanced carcinoid tumors in phase II studies. Objective response rates for sunitinib was 2.4% (one of 41 patients) [74]; for sorafenib 10% (4 of 41 patients) [77]; and with pazopanib no response was seen in 20 patients [78]. However, all studies report a relatively high rate of disease stabilization and potentially encouraging PFS duration (6-month PFS, 40% to 73%). These results could suggest that a cytostatic effect may be underappreciated when the primary efficacy endpoint is radiographic response in studies with VEGFR TKIs in carcinoid. Randomized studies will be needed to evaluate the activity of these TKIs in advanced carcinoid tumors.

Bevacizumab, which is a humanized monoclonal antibody that binds to circulating VEGF-A, has been evaluated in combination with octreotide long-acting release (LAR) in a randomized phase II trial in comparison to pegylated IFNa-2b in advanced carcinoid tumors [79]. After 18 weeks, 95 percent of patients treated with octreotide plus bevacizumab remained progression-free, compared with only 68 percent of those receiving octreotide plus IFNa-2b. Based on these results, SWOG has initiated a phase III trial investigating the efficacy of octreotide LAR plus either IFNa-2b or bevacizumab in patients with advanced carcinoid tumors. Bevacizumab has also been combined with different cytotoxic drugs (temozolomide, FOLFOX, capecitabine/oxaliplatin) in small phase II studies with objective response rates of 20-30% [80].

mTOR inhibitors

mTOR plays a central role in the proliferative effects of several growth factors, promotes cell metabolism and angiogenesis in part by mediating VEGF and insulin growth factor (IGF)-1 signaling. Two mTOR inhibitors, temsirolimus and everolimus, both rapamycin derivatives, have been evaluated in clinical trials for the treatment of patients with multiple types of malignancies including NETs.

A. mTOR inhibitors in pNETs

Temsirolimus as a single agent has been evaluated in a phase II study of 37 patients with advanced NET [81]. The response rate was only 5.6% and it was not pursued further as monotherapy. In recently reported preliminary results, the combination of temsirolimus (25mg IV weekly) with bevacizumab (10mg/kg every other week) in patients with well- or moderately-differentiated pNET and progressive disease by RECIST within 7 months of study entry showed encouraging activity. Confirmed PR was documented in 11 of the first 25 (44%) evaluable patients and 20 of 25 (80%) patients were progression-free at 6 months [82].

Everolimus has been studied extensively in NETs, with more than 1000 patients having been treated with it in clinical trials. The activity of everolimus in combination with octreotide long-acting (LAR) in patients with advanced low- to intermediate-grade neuroendocrine tumors was evaluated in a phase II study [83]. Among 30 patients with pNET, there were eight PRs (27%), 18 SDs (60%), and four PDs (13%). Median PFS was 50 weeks.

The activity of everolimus in pNET was explored in an international phase II study (RADIANT-1) of 160 patients with metastatic pNET whose disease had progressed during or after chemotherapy [84]. Patients were stratified by prior octreotide therapy (stratum 1: everolimus 10mg/d, n=115; stratum 2: everolimus 10mg/d plus octreotide long-acting release [LAR], n=45). Among patients receiving everolimus alone, the objective response rate was 10% and median PFS was 9.7 months. In patients who received octreotide plus everolimus, the partial response rate was 4% and median PFS was 17 months. The role of octreotide cannot be ascertained in this study as it was not randomized.

The activity of everolimus in pNETs was also evaluated in a large randomized phase III study. RADIANT-3 compared the efficacy of daily everolimus 10mg versus placebo, both in conjunction with best supportive care, in 410 patients with advanced progressing low- or intermediate-grade pNET [85]. The primary endpoint was progression-free survival in an intention-to-treat analysis. In the case of progression patients assigned to placebo could cross-over to open-label everolimus. The two groups were similar with respect to having previously received radiotherapy, chemotherapy and somatostatin analogue therapy. The median progression-free survival was significantly improved in the everolimus group: 11.0 months with everolimus as compared with 4.6 months with placebo (HR=0.35, $p<0.001$). In a pre-specified subgroup analysis, the benefit with everolimus was irrespective of prior chemotherapy, WHO performance status, age, sex, geogra-

phic region, prior somatostatin analogue therapy and tumor grade (either well- or moderately-differentiated). Confirmed objective tumor responses were observed in 10 patients receiving everolimus (5%), as compared to 4 patients receiving placebo (2%). Stable disease was evident in 73% of the patients in the everolimus group, as compared to 51% in the placebo group. Median overall survival was not reached at the time of analysis, and no significant difference between the groups was observed. However, 73% of the patients in the placebo arm crossed-over to treatment with everolimus upon progression, thus confounding the detection of any overall survival difference. Drug-related adverse events were mostly grade 1 or 2 and included stomatitis (in 64% of patients in the everolimus group vs. 17% in the placebo group); rash (49% vs. 10%); diarrhea (34% vs. 10%); fatigue (31% vs. 14%); and infections (23% vs. 6%), which were primarily of the upper respiratory. Grade 3 or 4 events that were more frequent with everolimus than with placebo included anemia (6% vs. 0%) and hyperglycemia (5% vs. 2%).

Based upon this study, everolimus is approved by the FDA and EMA for the treatment of progressive pancreatic NETs in patients with unresectable, locally advanced or metastatic disease.

B. mTOR inhibitors in carcinoids

The best evidence for the activity of mTOR inhibitors, specifically of everolimus, in patients with carcinoids comes from the RADIANT2 phase III trial [86]. The aim of this study was to evaluate whether everolimus at a dose of 10mg per day plus 30mg octreotide LAR every 28 days compared with placebo plus 30mg octreotide LAR every 28 days, prolongs progression-free survival in patients with well- or moderately-differentiated advanced neuroendocrine tumors and symptoms of carcinoid syndrome. 429 patients with progressive disease within 12 months prior to study entry were included. The patient population was heterogeneous, with small intestine primaries comprising about 50% of the population, while other primary sites included lung, colon, pancreas and even unknown primary sites. Median progression-free survival by central review was 16.4 (95% CI 13.7-21.2) months in the everolimus plus octreotide LAR group and 11.3 (8.4-14.6) months in the placebo plus octreotide LAR group (hazard ratio 0.77, 95% CI 0.59-1.00; one-sided log-rank test p=0.026). Adjusted for two interim analyses, the pre-specified boundary at final analysis was $p \leq 0.0246$, thus this study narrowly missed statistical significance and everolimus is not approved for extrapancreatic NETs. Most adverse events associated with everolimus plus octreotide LAR were grade 1 or 2 and consistent with the known safety profiles of these drugs. The most common drug-related adverse events of any grade were stomatitis (62%), rash (37%), fatigue (31%), and diarrhea (27%). The incidence of drug-related pneumonitis was 8% (18 patients) in the everolimus plus octreotide LAR group versus 0% in the placebo plus octreotide LAR group. In a recent preliminary report of a multivariate analysis of RADIANT-2, factors associated with a greater likelihood of response include non-elevated baseline CGA levels, WHO PS 0, absence of bone metastases, and lung as primary site [87]. Taking in account the lack of effective systemic treatments for advanced progressing carcinoid tumors and the results of the RADIANT-2 study, everolimus could be considered as a treatment option when other therapies have failed.

Other targeted pathways

The EGFR pathway has been targeted in NETs with limited success. In a study of gefitinib in 96 GEP-NET patients, response rates were less than 7% and at 6 months, 61% of patients with carcinoid tumors and 31% with pNET were progression-free [88]. Another tyrosine kinase receptor that is overexpressed in NETs is IGF-1R and targeted therapies are undergoing evaluation, including AMG479 (ganitumab) and cixutumumab. Other targeted agents that are under evaluation include brivanib (dual inhibitor of fibroblast growth factor and VEGF) and cabozantinib (MET and VEGFR2 inhibitor) [70].

Peptide receptor targeted radiotherapy (PRRT)

In the past two decades there has been substantial interest in targeted radiotherapy using radiolabeled somatostatin analogs. The radionuclides most commonly used are yttrium (^{90}Y) and lutetium (^{177}Lu), which differ in emitted particles, particle energy and tissue penetration. PRRT can be considered in both functioning and nonfunctioning NET with positive SRS, irrespective of the primary tumor site. Although there are no randomized studies, promising results have been reported with PRRT in patients with metastases from NETs, with response rates up to 37% mostly in small retrospective studies. It appears that response rates are higher in pancreatic tumors than in midgut NETs. In the largest series reported, 90Y-DOTA tyr3-octreotide was given to 1109 patients with metastatic NET and disease progression within 12 months, with positive somatostatin receptor scintigraphy. After the initial dose, additional treatment was withheld if there was disease progression or permanent toxicity. The number of courses delivered ranged from one to ten. The morphological response rate was 34.1%, while biochemical response was seen in 15.5% of the patients and 29.7% of the patients had symptomatic improvement [89]. The median survival from diagnosis was 94.6 months. Cox regression analyses revealed that longer survival was found with all types of responses. Overall, 142 patients (12.8%) developed grade 3 to 4 transient hematological toxicities, and 103 patients (9.2%) experienced grade 4 to 5 permanent renal toxicity. Multivariable analysis revealed that tumoral uptake in the initial imaging study was predictive for overall survival, whereas the initial kidney uptake was predictive for severe renal toxicity. Another radiolabeled somatostatin analogue that has been utilized is ^{177}Lu-DOTA, Tyr^3-octreotate and in one

report, over 500 patients were treated up to a cumulative dose of 750 to 800mCi (27.8-29.6GBq), usually in four treatment cycles, with treatment intervals of 6 to 10 weeks. The response rate in 310 evaluable patients was 30% [90]. Median OS from start of treatment was 46 months, while median OS from diagnosis was 128 months. Serious adverse events that were likely attributable to the treatment were myelodysplastic syndrome in three patients, and temporary, nonfatal, liver toxicity in two patients.

It appears that PRRT is a promising tool in the management of patients with advanced NETs, with manageable toxicity and is currently used in several European centers. However, the exact role of PRRT remains to be defined and well-designed studies comparing PRRT with medical therapy are needed.

CONCLUSION

Neuroendocrine tumors are relatively rare and include a diverse group of tumors with varied biological behavior. The incidence of neuroendocrine tumors appears to be increasing, but survival of patients with metastatic disease has improved. There is significant progress in the diagnosis and classification of these tumors. Surgery is the only curative therapy for patients with this disease. The available therapeutic options available are rapidly evolving. Therapy with somatostatin analogues is an efficient treatment to achieve palliation of symptoms, but also seems to have antiproliferative activity. Hepatic metastases, depending on size, number, and location, may be amenable to surgical resection, transarterial chemoembolization, or radiofrequency ablation. Recently, biological treatments that include radiolabeled somatostatin analogues, angiogenesis inhibitors, and mammalian target of rapamycin inhibitors show activity. Other targeted agents are under clinical investigation and are likely to play prominent roles in the management of neuroendocrine malignancies in the future.

Conflict of interest statement

The authors declare no conflict of interest.

REFERENCES

1. Kulke MH, Benson AB 3rd, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, et al. Neuroendocrine Tumors. Clinical Practice Guidelines in Oncology. JNCCN 2012; 10(6):724-764.
2. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008 Jun 20; 26(18):3063-72.
3. Oberg K, Castellano D. Current knowledge on diagnosis and staging of neuroendocrine tumors. Cancer Metastasis Rev 2011; 30(Suppl. 1):3-7.
4. Kuiper P, Verspaget HW, Overbeek LI, Biemond I, Lamers CB. An overview of the current diagnosis and recent developments in neuroendocrine tumours of the gastroenteropancreatic tract: the diagnostic approach. Neth J Med 2011; 69(1):14-20.
5. Öberg K, Knigge U, Kwekkeboom D, Perren A. ESMO Guidelines Working Group. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012 Oct; 23(Suppl. 7):vii124-30.
6. Jensen RT, Cadiot G, Brandi ML, de Herder WW, Kaltsas G, Komminoth P, et al. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms: functional pancreatic endocrine tumor syndromes. Neuroendocrinology 2012; 95(2):98-119.
7. Klöppel G. Classification and pathology of gastroenteropancreatic neuroendocrine neoplasms. Endocr Relat Cancer 2011; 18(Suppl. 1):S1-16.
8. Klöppel G, Couvelard A, Perren A, Komminoth P, McNicol AM, Nilsson O, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification. Neuroendocrinology 2009; 90(2):162-6.
9. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. Pancreas 2010; 39(6):707-12.
10. Jann H, Roll S, Couvelard A, Hentic O, Pavel M, Müller-Nordhorn J, et al. Neuroendocrine tumors of midgut and hindgut origin: tumor-node-metastasis classification determines clinical outcome. Cancer 2011; 117(15):3332-41.
11. Yang Z, Tang LH, Klimstra DS. Effect of tumor heterogeneity on the assessment of Ki67 labeling index in well-differentiated neuroendocrine tumors metastatic to the liver: implications for prognostic stratification. Am J Surg Pathol 2011; 35(6):853-60.
12. Oberg K. Circulating biomarkers in gastroenteropancreatic neuroendocrine tumours. Endocr Relat Cancer 2011 Oct 17; 18(Suppl. 1):S17-25.
13. O'Toole D, Grossman A, Gross D, Delle Fave G, Barkmanova J, O'Connor J, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: biochemical markers. Neuroendocrinology 2009; 90(2):194-202.
14. Arnold R, Wilke A, Rinke A, Mayer C, Kann PH, Klose KJ, et al. Plasma chromogranin A as marker for survival in patients with metastatic endocrine gastroenteropancreatic tumors. Clin Gastroenterol Hepatol 2008; 6(7):820-7.
15. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol 2008; 9(1):61-72.
16. Bhattacharyya S, Toumpanakis C, Caplin ME, Davar J. Usefulness of N-terminal pro-brain natriuretic peptide as a biomarker of the presence of carcinoid heart disease. Am J Cardiol 2008; 102(7):938-42.
17. Modlin IM, Gustafsson BI, Drozdov I, Nadler B, Pfragner R, Kidd M. Principal component analysis, hierarchical clustering, and decision tree assessment of plasma mRNA and hormone levels as an early detection strategy for small intestinal neuroendocrine (carcinoid) tumors. Ann Surg Oncol 2009; 16(2): 487-98.
18. Arnold R, Chen YJ, Costa F, Falconi M, Gross D, Grossman AB, et al. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: follow-up and documentation. Neuroendocrinology 2009; 90(2):227-33.
19. Sundin A, Vullierme MP, Kaltsas G, Plöckinger U; Mallorca Consensus Conference participants; European Neuroendocrine Tumor Society. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. Neuroendocrinology 2009; 90(2):167-83.
20. Johanssen S, Boivin M, Lochs H, Voderholzer W. The yield of wireless capsule endoscopy in the detection of neuroendocrine tumors in comparison with CT enteroclysis. Gastrointest Endosc 2006; 63(4):660-5.
21. Teunissen JJ, Kwekkeboom DJ, Valkema R, Krenning EP. Nuclear medicine techniques for the imaging and treatment of neuroendocrine tumours. Endocr Relat Cancer 2011; 18(Suppl. 1):S27-51.

22. Belhocine T, Foidart J, Rigo P, Najjar F, Thiry A, Quatresooz P, et al. Fluorodeoxyglucose positron emission tomography and somatostatin receptor scintigraphy for diagnosing and staging carcinoid tumours: correlations with the pathological indexes p53 and Ki-67. Nucl Med Commun 2002; 23(8):727-34.

23. Kayani I, Bomanji JB, Groves A, Conway G, Gacinovic S, Win T, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTATATE (DOTA-DPhe1, Tyr3-octreotate) and 18F-FDG. Cancer 2008; 112(11):2447-55.

24. Zarebczan B, Chen H. Signaling mechanisms in neuroendocrine tumors as targets for therapy. Endocrinol Metab Clin North Am 2010; 39(4):801-10.

25. Chen M, Van Ness M, Guo Y, Gregg J. Molecular pathology of pancreatic neuroendocrine tumors. J Gastrointest Oncol 2012; 3(3):182-8.

26. Turaga KK, Kvols LK. Recent progress in the understanding, diagnosis, and treatment of gastroenteropancreatic neuroendocrine tumors. CA Cancer J Clin 2011; 61(2):113-32.

27. Gilligan CJ, Lawton GP, Tang LH, et al. Gastric carcinoid tumors: the biology and therapy of an enigmatic and controversial lesion. Am J Gastroenterol 1995; 90:338-352.

28. Delle Fave G, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, et al. ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. Neuroendocrinology 2012; 95(2):74-87.

29. Pape UF, Perren A, Niederle B, Gross D, Gress T, Costa F, et al. ENETS Consensus Guidelines for the management of patients with neuroendocrine neoplasms from the jejuno-ileum and the appendix including goblet cell carcinomas. Neuroendocrinology 2012; 95(2):135-56.

30. Bilimoria KY, Bentrem DJ, Merkow RP, et al. Application of the pancreatic adenocarcinoma staging system to pancreatic neuroendocrine tumors. J Am Coll Surg 2007; 205:558.

31. Fernández-Cruz L, Blanco L, Cosa R, Rendón H. Is laparoscopic resection adequate in patients with neuroendocrine pancreatic tumors? World J Surg 2008; 32:904-17.

32. Parekh JR, Wang SC, Bergsland EK, Venook AP, Warren RS, Kim GE, et al. Lymph node sampling rates and predictors of nodal metastasis in pancreatic neuroendocrine tumor resections: the UCSF experience with 149 patients. Pancreas 2012; 41(6):840-4.

33. Sarmiento JM, Que FG. Hepatic surgery for metastases from neuroendocrine tumors. Surg Oncol Clin N Am 2003; 12:231-42.

34. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003; 197:29-37.

35. Dousset B, Saint-Marc O, Pitre J, Soubrane O, Houssin D, Chapuis Y. Metastatic endocrine tumors: medical treatment, surgical resection, or liver transplantation. World J Surg 1996; 20:908-914.

36. Mayo SC, de Jong MC, Pulitano C, Clary BM, Reddy SK, Gamblin TC, et al. Surgical management of hepatic neuroendocrine tumor metastasis: results from an international multi-institutional analysis. Ann Surg Oncol 2010; 17:3129-36.

37. Swärd C, Johanson V, Nieveen van Dijkum E, Jansson S, Nilsson O, Wängberg B, et al. Prolonged survival after hepatic artery embolization in patients with midgut carcinoid syndrome. Br J Surg 2009; 96:517-21.

38. Gupta S, Johnson MM, Murthy R, Ahrar K, Wallace MJ, Madoff DC, et al. Hepatic arterial embolization and chemoembolization for the treatment of patients with metastatic neuroendocrine tumors: variables affecting response rates and survival. Cancer 2005; 104:1590-602.

39. King J, Quinn R, Glenn DM, Janssen J, Tong D, Liaw W, et al. Radioembolization with selective internal radiation microspheres for neuroendocrine liver metastases. Cancer 2008; 113:921-9.

40. Kennedy AS, Dezarn WA, McNeillie P, Coldwell D, Nutting C, Carter D, et al. Radioembolization for unresectable neuroendocrine hepatic metastases using resin 90Y-microspheres: early results in 148 patients. Am J Clin Oncol 2008; 31:271-9.

41. Liu DM, Kennedy A, Turner D, Rose SC, Kee ST, Whiting S, et al. Minimally invasive techniques in management of hepatic neuroendocrine metastatic disease. Am J Clin Oncol 2009; 32:200-215.

42. Gedaly R, Daily MF, Davenport D, McHugh PP, Koch A, Angulo P, et al. Liver transplantation for the treatment of liver metastases from neuroendocrine tumors: an analysis of the UNOS database. Arch Surg 2011; 146:953-8.

43. Modlin IM, Pavel M, Kidd M, Gustafsson BI. Review article: Somatostatin analogues in the treatment of gastroenteropancreatic neuroendocrine (carcinoid) tumours. Aliment Pharmacol Ther 2010; 31:169-188.

44. Pavel M, Baudin E, Couvelard A, Krenning E, Öberg K, Steinmüller T, et al.; Barcelona Consensus Conference participants. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012; 95(2):157-76.

45. Ramage JK, Ahmed A, Ardill J, Bax N, Breen DJ, Caplin ME, et al. UK and Ireland Neuroendocrine Tumour Society Guidelines for the management of gastroenteropancreatic neuroendocrine (including carcinoid) tumours (NETs). Gut 2012 Jan; 61(1):6-32.

46. Schmid HA, Schoeffter P. Functional activity of the multiligand analog SOM230 at human recombinant somatostatin receptor subtypes supports its usefulness in neuroendocrine tumors. Neuroendocrinology 2004; 80(Suppl. 1):47-50.

47. Kvols LK, Oberg KE, O'Dorisio TM, Mohideen P, de Herder WW, Arnold R, et al. Pasireotide (SOM230) shows efficacy and tolerability in the treatment of patients with advanced neuroendocrine tumors refractory or resistant to octreotide LAR: results from a phase II study. Endocr Relat Cancer 2012; 19(5):657-66.

48. di Bartolomeo M, Bajetta E, Buzzoni R, Mariani L, Carnaghi C, Somma L, et al. Clinical efficacy of octreotide in the treatment of metastatic neuroendocrine tumors. A study by the Italian Trials in Medical Oncology Group. Cancer 1996; 77:402-8.

49. Rinke A, Müller HH, Schade-Brittinger C, Klose KJ, Barth P, Wied M, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009; 27:4656-63.

50. Faiss S, Pape UF, Böhmig M, Dörffel Y, Mansmann U, Golder W, et al.; International Lanreotide and Interferon Alfa Study Group. Prospective, randomized, multicenter trial on the antiproliferative effect of lanreotide, interferon alfa, and their combination for therapy of metastatic neuroendocrine gastroenteropancreatic tumors - the International Lanreotide and Interferon Alfa Study Group. J Clin Oncol 2003; 21:2689-2696.

51. Arnold R, Rinke A, Klose KJ, Müller HH, Wied M, Zamzow K, et al. Octreotide versus octreotide plus interferon in endocrine gastroenteropancreatic tumors: a randomized trial. Clin Gastroenterol Hepatol 2005; 3:761-771.

52. Detjen KM, Welzel M, Farwig K, Brembeck FH, Kaiser A, Riecken EO, et al. Molecular mechanism of interferon alfa-mediated growth inhibition in human neuroendocrine tumor cells. Gastroenterology 2000; 118(4):735-48.

53. Kölby L, Persson G, Franzén S, Ahrén B. Randomized clinical trial of the effect of interferon alpha on survival in patients with disseminated midgut carcinoid tumours. Br J Surg 2003; 90(6):687-93.

54. Öberg K. Interferon in the management of neuroendocrine GEP tumors. Digestion 2000; 62(Suppl. 1):92-7.

55. Broder LE, Carter SK. Pancreatic islet cell carcinoma. II. Results of therapy with streptozotocin in 52 patients. Ann Intern Med 1973; 79(1):108-18.

56. Moertel CG, Hanley JA, Johnson LA. Streptozocin alone compared with streptozocin plus fluorouracil in the treatment of advanced islet-cell carcinoma. N Engl J Med 1980; 303:1189-94.

57. Moertel CG, Lefkopoulo M, Lipsitz S, Hahn RG, Klaassen D. Streptozocin-doxorubicin, streptozocin- fluorouracil or chlorozotocin in the treatment of advanced islet-cell carcinoma. N Engl J Med 1992; 326:519-23.

58. Kouvaraki MA, Ajani JA, Hoff P, Wolff R, Evans DB, Lozano R, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22(23):4762-71.

59. Ramanathan RK, Cnaan A, Hahn RG, Carbone PP, Haller DG. Phase II trial of dacarbazine (DTIC) in advanced pancreatic islet cell carcinoma. Study of the Eastern Cooperative Oncology Group-E6282. Ann Oncol 2001; 12(8):1139-43.

60. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line che-

motherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer 2011; 117(2):268-75.
61. Ansell SM, Pitot HC, Burch PA, Kvols LK, Mahoney MR, Rubin J. A phase II study of high-dose paclitaxel in patients with advanced neuroendocrine tumors. Cancer 2001; 91:1543-8.
62. Kulke MH, Kim H, Clark JW, Enzinger PC, Lynch TJ, Morgan JA, et al. A phase II trial of gemcitabine for metastatic neuroendocrine tumors. Cancer 2004; 101:934-9.
63. Chan JA, Zhu AX, Stuart K, Bhargava P, Earle CC, Clark JW, et al. Phase II study of pemetrexed in patients with advanced neuroendocrine tumors. Cancer Chemother Pharmacol 2010; 66:961-8.
64. Ansell SM, Mahoney MR, Green EM, Rubin J. Topotecan in patients with advanced neuroendocrine tumors: a phase II study with significant hematologic toxicity. Am J Clin Oncol 2004; 27:232-5.
65. Engstrom PF, Lavin PT, Moertel CG, Folsch E, Douglass HO Jr. Streptozocin plus fluorouracil versus doxorubicin therapy for metastatic carcinoid tumor. J Clin Oncol 1984; 2:1255-9.
66. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG; Eastern Cooperative Oncology Group. Phase II/III study of doxorubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol 2005; 23:4897-904.
67. Kulke MH, Hornick JL, Frauenhoffer C, Hooshmand S, Ryan DP, Enzinger PC, et al. O6-methylguanine DNA methyltransferase deficiency and response to temozolomide-based therapy in patients with neuroendocrine tumors. Clin Cancer Res 2009; 15(1):338-45.
68. Brizzi MP, Berruti A, Ferrero A, Milanesi E, Volante M, Castiglione F, et al. Continuous 5-fluorouracil infusion plus long acting octreotide in advanced well-differentiated neuroendocrine carcinomas. A phase II trial of the Piemonte Oncology Network. BMC Cancer 2009; 9:388.
69. Bajetta E, Catena L, Procopio G, De Dosso S, Bichisao E, Ferrari L, et al. Are capecitabine and oxaliplatin (XELOX) suitable treatments for progressing low-grade and high grade neuroendocrine tumours? Cancer Chemother Pharmacol 2007; 59:637-642.
70. Karpathakis A, Caplin M, Thirlwell C. Hitting the target: where do molecularly targeted therapies fit in the treatment scheduling of neuroendocrine tumours? Endocr Relat Cancer 2012; 19(3):R73-92.
71. Zhang J, Jia Z, Li Q, Wang L, Rashid A, Zhu Z, et al. Elevated expression of vascular endothelial growth factor correlates with increased angiogenesis and decreased progression-free survival among patients with low-grade neuroendocrine tumors. Cancer 2007; 109:1478-86.
72. Missiaglia E, Dalai I, Barbi S, Beghelli S, Falconi M, della Peruta M, et al. Pancreatic endocrine tumors: expression profiling evidences a role for AKT-mTOR pathway. J Clin Oncol 2010; 28:245-55.
73. Pitt SC, Davis R, Kunnimalaiyaan M, Chen H. AKT and PTEN expression in human gastrointestinal carcinoid tumors. Am J Transl Res 2009; 1:291-9.
74. Kulke MH, Lenz HJ, Meropol NJ, Posey J, Ryan DP, Picus J, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008; 26:3403-10.
75. Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011; 364:501-13.
76. Phan AT. Metastatic pancreatic neuroendocrine tumors (pNET): Placing current findings into perspective. Cancer Treat Rev 2013; 39(1):3-9.
77. Hobday TJ, Rubin J, Holen K, et al. MC044h, a phase II trial of sorafenib in patients (pts) with metastatic neuroendocrine tumors (NET): a phase II consortium (P2C) study. J Clin Oncol 2007; 25:18s (suppl.; abstr 4505).
78. Phan A, Yao J, Fogelman D, et al. A prospective, multi-institutional phase II study of GW786034 (pazopanib) and depot octreotide (sandostatin LAR) in advanced low-grade neuroendocrine carcinoma (LGNEC). J Clin Oncol 2010; 28:18s (suppl.; abstr 4044).
79. Yao JC, Phan A, Hoff PM, Chen HX, Charnsangavej C, Yeung SC, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. J Clin Oncol 2008; 26:1316-23.
80. Oberg K. Neuroendocrine tumors of the digestive tract: impact of new classifications and new agents on therapeutic approaches. Curr Opin Oncol 2012; 24(4):433-40.
81. Duran I, Kortmansky J, Singh D, Hirte H, Kocha W, Goss G, et al. A phase II clinical and pharmacodynamic study of temsirolimus in advanced neuroendocrine carcinomas. Br J Cancer 2006; 95:1148-54.
82. Hobday TJ, Qin R, Reidy DL, et al. Multicenter phase II trial of temsirolimus and bevacizumab in pancreatic neuroendocrine tumor (abstract). J Clin Oncol 2012; 30 (Suppl. 4): abstract 260.
83. Yao JC, Phan AT, Chang DZ, Wolff RA, Hess K, Gupta S, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low- to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol 2008; 26(26):4311-8.
84. Yao JC, Lombard-Bohas C, Baudin E, Kvols LK, Rougier P, Ruszniewski P, et al. Daily oral everolimus activity in patients with metastatic pancreatic neuroendocrine tumors after failure of cytotoxic chemotherapy: a phase II trial. J Clin Oncol 2010; 28:69-76.
85. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011; 364:514-23.
86. Pavel M, Hainsworth JD, Baudin E, Peeters M, Hoersch D, Winkler R, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet 2011; 378(9808):2005-12.
87. Yao JC, Hainsworth JD, Wolin EM, et al. Multivariate analysis including biomarkers in the phase III RADIANT-2 study of octreotide LAR plus everolimus or placebo among patients with advanced neuroendocrine tumors (abstract). J Clin Oncol 2012; 30 (Suppl. 4): abstract 157.
88. Hobday TJ, Holen K, Donehower R, et al. A phase II trial of gefitinib in patients (pts) with progressive metastatic neuroendocrine tumors (NET): a phase II consortium (P2C) study. ASCO Annual Meeting Proceedings 2006; 24(18 Suppl.): abstract 4043.
89. Imhof A, Brunner P, Marincek N, Briel M, Schindler C, Rasch H, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. J Clin Oncol 2011; 29(17):2416-23.
90. Kwekkeboom DJ, de Herder WW, Kam BL, van Eijck CH, van Essen M, Kooij PP, et al. Treatment with the radiolabeled somatostatin analog [177 Lu-DOTA 0,Tyr3]octreotate: toxicity, efficacy, and survival. J Clin Oncol 2008; 26:2124-30.

Colonic metastasis of renal cell carcinoma 4 months after left radical nephrectomy: A case report and a review of post-nephrectomy colonic metastases from renal cell cancer

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ABSTRACT

Renal cell carcinoma is one of the most common malignancies of the genitourinary tract. A 64 year-old man, with medical history significant for left radical nephrectomy due to renal cell cancer, presented to our Department due to symptoms of colicky abdominal pain and sense of flatulence, which started 1 month earlier. Right colectomy was performed and the histological findings of the tumor revealed metastatic disease from the renal cell cancer. A comprehensive Medline search revealed only 11 reported cases to date, of post-nephrectomy colonic metastasis from renal cell cancer -in one case there was also a simultaneous duodenal mass- while in another 2 cases there was a synchronous metastatic disease in colon at the diagnosis of the disease. In patients with personal history significant for renal cell cancer, the occurrence of colon metastasis should always be excluded, on presence of either clinical indication or imaging findings in colon. To the best of our knowledge, this case represents the first incidence of early solitary colonic metastasis of renal cell cancer, only 4 months after radical nephrectomy.

Key words: renal mass; renal cell carcinoma; colonic metastases; intraluminal metastatic mass; metastatic renal cell carcinoma; post-nephrectomy colonic metastasis; solitary metachronous RCC metastases in colon.

INTRODUCTION

Renal cell cancer, a term that includes a variety of cancers arising in the kidney, comprises several histologically, biologically, and clinically distinct entities, which accounts for 3% of neoplasias in adults and the third most frequent neoplasia of the genitourinary system [1, 2]. The incidence in males is greater than it is in females, with a ratio of 1.6:1. Largely a disease of adulthood, with peak incidence after the fifth decade of life, RCC may also occur in children and infants [3]. Many renal masses are found incidentally during evaluation of unrelated medical issues or metastatic foci. Only 10% of patients present with the classic triad of hematuria, pain and flank mass [4, 5]. Initial presentation may also be a paraneoplasmatic syndrome or laboratory abnormality, including elevated erythrocyte sedimentation rate, weight loss, cachexia, hypertension from increased renin, anemia, hypercalcemia (release of PTH-like substance), elevated alkaline phosphatase, polycythemia (increased erythropoietin), and Stauffer's syndrome (reversible, non-metastatic hepatic dysfunction that usually resolves once the primary tumor is removed) [6-8]. Approximately one out of four patients appears with metastatic disease [9, 10]. Common sites of metastatic spread include lung (70%-75%), lymph nodes (30%-40%) and bone (20%-25%) while the liver, the central nervous system and the soft tissues are less commonly affected. Particularly, the onset of metastasis in the intestine is unusual. Thus, metastatic disease in the colon is extremely rare [11]. To the best of our knowledge, this case represents the first incidence of early solitary colonic metastasis of renal cell cancer, only 4 months after nephrectomy.

MATERIAL & METHODS - CASE PRESENTATION

A 64 year-old man presented to our Depart-

ment due to symptoms of colicky abdominal pain and sense of flatulence, which had started one month earlier. He did not mention any recent change in bowel habit, rectal bleeding, melena or constipation. He had no fever. His medical history was significant for radical nephrectomy of the left kidney four months earlier because of a renal mass.

At that time, the patient had been admitted to the hospital because of abdominal pain which reflected to the loin, having appeared a month earlier. Also, he had noticed a 4kg weight-loss in the previous two months. No symptoms or signs of pyrexia, macroscopic or microscopic hematuria, hematochezia/melena or change in bowel habits had been noted. The Complete Blood Count and basic serum biochemistry were within normal limits. Due to no abnormal ultrasound findings of solid organs, urinary system and pelvis cavity, a CT scan of the abdomen (with p.os and i.v. contrast) had been performed. It revealed a 7×7×6 cm in size, left renal mass with heterogeneous constitution, mainly solid. The rest of the imaging evaluation, with CT scan of the chest -i.v. contrast agent had been administered- as well as a preoperative MRI of the abdomen -i.v. paramagnetic contrast agent had been administered- did not demonstrate any other pathological conditions affecting the chest or the abdomen. Histological examination of the tumor revealed renal cell carcinoma; 8cm; eosinophilic variant; grade II; not invading the perirenal fat, perirenal capsule, renal pelvis, ureteral and vascular stump. The immune-phenotype of the tumor was Vimentin (+):+, AE1/AE3:+, Ker7:- . Due to having been limited to the renal and in absence of any evidence for distant metastases -with regard to standard staging process of renal cell cancer- the stage of the tumor was T2NXM0. So, according to the international guidelines, the patient did not undergo adjuvant chemotherapy but was placed in a strict follow-up at the outpatient clinic.

Four months later, physical examination and basic laboratory tests did not reveal any remarkable findings. Colonoscopy was performed and an obstructive intraluminal lesion near the hepatic flexure was discovered. Right colectomy was performed. The surgical specimen included part of terminal ileum (8.5 cm in length), in following with part of the colon (20.5 cm) and the appendix of 10.5 cm length. Macroscopically, 6cm after the ileocecal valve, a partially ulcerative neoplasia was noticed, whose extent over the intestinal mucosa was 7cm×5cm. Moreover, in histological sections of the described tumor, the image of an ulcerative malignant neoplasia was macroscopically identified with characteristics of a low differentiated carcinoma. The development pattern was formed by solid zones and islets, separated by thin fibrovascular tissue, composed with cells characterized by intensive nuclear and cellular atypia - the spectrum of nuclei morphology ranged from multiformity to generation of "bizarre" multilobular or multinuclear forms, accompanied with a satisfying number of mitoses, and eosinophilic cytoplasm. Alcian blue, PAS and dPAS stains did not demonstrate mucus production. The immune-phenotype of the tumor was AE1/AE3:+; CK7:+ CK20:-; S100:-; LCA:-; Chromogranin:-; Synaptophysin:- HMB45:-. Despite the macroscopic characteristics of a primary malignancy, the microscopic morphological, histochemical and immunophenotypic features support the diagnosis of metastatic disease rather than that of primary disease. The histological findings of the two neoplasias - renal and colon- were compared. In both cases, there were common morphological features, of oncocytic type renal cell cancer, with the only difference being the grade of differentiation, as the one in the colon was poor (intensive atypia, satisfying number of mitoses and necroses). In addition, the immunophenotypic and histochemical features are more compatible with renal malignancy, being simultaneously incompatible with primary colorectal cancer. The tumor invaded all layers of the intestinal wall, up to the pericolic fat. The surgical (proximal, distal and lateral) margins and the 52 dissected lymph nodes were free of disease. In a recent follow-up, the patient appears to be in good physical condition without evidence of disease.

RESULTS

A comprehensive Medline search revealed only 11 reported cases to date, of post-nephrectomy colonic metastasis from renal cell cancer [12, 13, 14, 15-21] -in one case there was also a simultaneous duodenal mass- while in other 2 cases there was a synchronous metastatic disease in colon at the diagnosis of the disease [22, 23] (Table 1).

DISCUSSION

Renal cell carcinoma is one of the most common malignancies of the genitourinary tract [24]. The biological behavior of RCC is characteristically variable and the prognosis is unpredictable [25]. The clinical course of the disease ranges from months to several decades and even spontaneous regression has been documented [26]. In approximately one third of patients, distant metastases are present at the time of initial diagnosis and in another third, the tumor will recur even after nephrectomy with a curative intent [27]. Renal cell carcinoma can disseminate locally by contiguity and metastasize to distant sites. In addition, renal carcinomas are noted for causing "late" metastases at unusual sites such as the skin, eyes and even tongue several years after removal of the primary tumor. The delayed occurrence (as late as 31 years after a nephrectomy) of metastatic RCC is well known [12]. Solitary metachronous metastases from RCC are rare; however, they can occur very late in the course of the disease [28, 29]. Therefore, careful long-term follow-up may be beneficial for patients with a history of RCC even after undergoing a curative nephrectomy [13, 14]. Renal cell carcinoma may metastasize to almost every organ of the body, but 95% of the metastatic lesions involve the lung, lymph nodes, liver, bone,

Table 1.

A comprehensive Medline search revealed only 11 reported cases to date, of post-nephrectomy colonic metastasis from renal cell cancer. The table makes a reference to patient gender; their age at the time of diagnosis; the kind of nephrectomy (left or right); the first symptom that led to diagnosis; the time after nephrectomy; and the place of colon that the metastatic disease appeared.

AUTHOR	GENDER	AGE	NEPHRECTOMY	SYMPTOM	POST-NEPHRECTOMY TIME	SECTION OF COLON
THOMASON	♀	71	LEFT	Abdominal pain	17 years	Descending
RUIZ	♂	73	LEFT	Obstruction	11 years	Transverse
TOKONABE	♂	83	RIGHT	Melena, abdominal mass	7 years	Transverse
TARRERIAS 1st	♂	62	LEFT	Bleeding from rectum	5 years	Sigmoid
TARRERIAS 2nd	♂	72	LEFT	Iron deficiency anemia	4 years	Ascending
DIAZ	♂	73	LEFT	Hematochezia, Melena	8 years	Sigmoid
UTSUNORIKA	♂	47	LEFT	Hematochezia	9 years	Transverse
LEE	♀	76	LEFT	Dyspnea, Right costal margin pain	4 years	Ascending
YETKIN	♂	60	RIGHT	Dyspnea, Right costal margin pain	5 years	Hepatic flexure
VALDESPINO	♂	60		Hematochezia	8 years	Splenic flexure
JADAV	♀	65	LEFT	Acute abdominal pain, flatulence	9 years	Transverse
ASIMAKOPOULOS	♂	64	LEFT	Abdominal pain	4 months	Ascending

adrenal glands and the opposite kidney. With regard to the gastrointestinal tract, metastasis is surprisingly uncommon and is restricted to single case reports. Particularly, renal cell cancer very rarely metastasizes to the colon. Surgical excision of the local recurrence is the best procedure for therapy, but this can be radical only when the recurrence can be completely excised [12, 21, 30]. Chemotherapies, including hormonal and interferon therapies, are effective in some patients with metastatic renal cell carcinoma [25]. As is mentioned above, a comprehensive Medline search revealed only 11 reported cases to date, of post-nephrectomy colonic metastasis from renal cell cancer [12, 13, 14, 15-21] -in one case there was also a simultaneous duodenal mass- while in other 2 cases there was a synchronous metastatic disease in the colon at disease diagnosis [22, 23]. If the current case is included, then the average age for the occurrence of the colonic metastasis reaches 67 years old (range from 47 to 92 years), while the average time post-nephrectomy is 7.3 years (range from 4 months to 17 years). In the majority of cases, it concerns males (9 males: 3 females) that underwent a left radical nephrectomy in the past (9 left: 2 right radical nephrectomies, while 1 remained undefined by the authors). Furthermore, most renal cell carcinomas that involve the colon result in large, solitary tumor masses with characteristic morphology, that cause remarkable clinical presentation, such as acute abdominal pain, palpable abdominal mass, melena, hematochezia, flatulence, dyspnea and iron deficiency anemia [12-23]. Nevertheless, we wish to draw attention to one case of subtle intramucosal colonic involvement resulting in multiple small colonic polyps, which were clinically asymptomatic [31]. In every case the metastatic tumor was surgically excluded. In contrast to all cases reported so far, in this clinical case it is significant that the intraluminal mass appeared only four months after the radical nephrectomy. To conclude with, in patients with personal history significant for renal cell cancer, the occurrence of colon metastasis should always be excluded, on presence of either clinical indication (such as abdominal pain, melena, hematochezia, palpable mass, iron-deficiency anemia etc.) or imaging findings in the colon (such as intraluminal mass/tumor). As was mentioned before, to the best of our knowledge, this case represents the first incidence of early solitary colonic metastasis of renal cell cancer, only 4 months after radical nephrectomy, presenting in the way of abdominal pain.

Conflict of interest statement

The authors declare no conflict of interest.

REFERENCES

1. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. Lancet 2009; 373(9669):1119-32. doi: 10.1016/S0140-6736(09)60229-4.
2. McNichols DW, Segura JW. Renal cell carcinoma - long term survival and late recurrence. J Urol 1981; 126:17-23.
3. Surveillance Epidemiology and End Results. SEER Stat Fact Sheets. National Cancer Institute. Available at http://seer.cancer.gov/statfacts/html/kidrp.html. Accessed February 2, 2010.
4. Skinner DG, Colvin RB, Vermillion CD, et al. Diagnosis and management of renal cell carcinoma. A clinical and pathologic study of 309 cases. Cancer 1971; 28:1165.
5. DeKernion JB. Real numbers. In: Campbell's Urology. Walsh, PC, Gittes, RF, Perlmutter, AD (Eds), WB Saunders, Philadelphia 1986; p. 1294.
6. Jonasch, et al. In: Kantarjian HM, Wolff RA, Koller CA, eds. Renal cell carcinoma. MD Anderson Manual of Medical Oncology. New York, NY: McGraw-Hill; 2006.
7. Linehan MW, Berton Z, Bates S. In: Devita VT Jr, Hellman S, Rosenberg SA, eds. Cancer of kidney and ureter. Principles and Practice of Oncology. 6th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2001: 1362-96.
8. Simon JW, Marshall FF. In: Abeloff MD, Armitage J, Niederhuber J, Kastan M, McKenna W, eds. Kidney and ureter. Clinical Oncology. 2nd ed. New York, NY: Churchill Livingstone; 2000: 1784-99.
9. Toh SKC, Hale JE. Late presentation of a solitary metastasis of renal cell carcinoma as an obstructive duodenal mass. Postgrad Med J 1996; 72:178-179.
10. Garnick, MB. Primary neoplasms of the kidney. In: Therapy in Nephrology and Hypertension: A Companion to Brenner and Rector's the Kidney, Brady, HR, Wilcox, CS (Eds), WB Saunders, Philadelphia 1998.
11. Saitoh H. Distant metastasis of renal adenocarcinoma. Cancer 1981 Sep 15; 48(6):1487-91.
12. Thomason PA, Peterson LS, Staniunas RJ. Solitary colonic metastasis from renal-cell carcinoma 17 years after nephrectomy. Dis Colon Rectum 1991; 34:709-712.
13. Utsunomiya K, Yamamoto H, Koiwai H, Kirii Y, Kashiwagi H, Konishi F, Kurihara K, Kawai T, Sugano K. Solitary colonic metastasis from renal cell carcinoma 9 years after nephrectomy: report of a case. Int J Colorectal Dis 2001; 16(3):193-4.
14. Yetkin G, Uludag M, Ozagari A. Solitary colonic metastasis of renal cell carcinoma. Acta Chirurgica Belgica 2008; 108(2):264-5.
15. Ruiz JL, et al. Renal carcinoma: late recurrence in 2 cases. Eur Urol 1991; 20:167-169.
16. Tokonabe S, et al. Solitary colonic metastasis of renal cell carcinoma seven years after nephrectomy: a case report. Int J Urol 1996; 3(6):501-503.
17. Tarrerias AR, et al. Colonic metastasis from kidney cancer. Presentation of 2 cases. Gastroenter Clin Biol 1997; 21(3):228-229.
18. Diaz-Candamo MJ, et al. Colonic metastasis from renal cell carcinoma: helical- CT demonstration. Eur Radiol 2000; 10(1):139-140.
19. Lee JG, et al. Simultaneous duodenal and colon masses of late presentation of metastatic renal cell carcinoma. Korean J Intern Med 2002 Jun; 17(2):143-146.
20. Valdespino-Castillo VE, et al. Renal cell carcinoma with colonic metastases: an infrequent site for metastases. Cir Cir 2008 Jul-Aug; 76(4):339-342.
21. Jadav AM, et al. Solitary colonic metastasis from renal cell carcinoma presenting as a surgical emergency nine years post-nephrectomy. World J Surg Oncol 2010 Jun 29; 8:54.
22. Zerbib F, et al. Colonic metastasis of a renal cell carcinoma. A case report. Tumori 1992 Jun 30; 78(3):219-220.
23. Nozaki Y, et al. Metastatic tumor in the colon from renal cell carcinoma. Intern Med 2010; 49(7):709.
24. Aza Mohammed, Iqbal Shergill, and Brian Little. Expert Review of Molecular Diagnostics, January 2009, Vol. 9, No. 1, Pages 75-83.
25. Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med 1996; 335:865-875.
26. Hamid Y, Poller DN. Spontaneous regression of renal cell carcinoma: a pitfall in diagnosis of renal lesions. J Clin Pathol 1998; 51(4):334-336.
27. Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005; 353:2477-90.
28. Nakano E, Fujioka H, Matsuda M, Osafune M, Takaha M, Sonoda T. Late recurrence of renal cell carcinoma after nephrectomy. Eur Urol 1984; 10(5):347-9.
29. Jain V, Shergill GS, Gupta K, Bhandari RK. Case report: Renal cell carcinoma: Unusual metastases. Indian J Radiol Imaging 2000; 10:249-51.
30. Newmark JR, Newmark GM, Epstein JI, Marshall FF. Solitary late recurrence of renal cell carcinoma. Urology 1994; 43(5):725-8. doi: 10.1016/0090-4295(94)90199-6.
31. Chetty R, Syed A, van der Kwast T. Metastatic clear cell renal cell carcinoma presenting as multiple colonic polyps. Int J Surg Pathol 2011 Dec; 19(6):791-4.

ΣΥΝΟΠΤΙΚΗ ΠΕΡΙΛΗΨΗ ΤΩΝ ΧΑΡΑΚΤΗΡΙΣΤΙΚΩΝ ΤΟΥ ΠΡΟΪΟΝΤΟΣ. 1. ΟΝΟΜΑΣΙΑ ΤΟΥ ΦΑΡΜΑΚΕΥΤΙΚΟΥ ΠΡΟΪΟΝΤΟΣ: YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση. **2. ΠΟΙΟΤΙΚΗ ΚΑΙ ΠΟΣΟΤΙΚΗ ΣΥΝΘΕΣΗ:** Κάθε ml πυκνού διαλύματος περιέχει 5 mg ipilimumab. Ένα φιαλίδιο των 10 ml περιέχει 50 mg ipilimumab. Ένα φιαλίδιο των 40 ml περιέχει 200 mg ipilimumab. Το ipilimumab είναι ένα πλήρως ανθρώπινο αντι CTLA4 μονοκλωνικό αντίσωμα (IgG1κ) που παράγεται σε κύτταρα ωοθηκών κινεζικού κρικητού με τεχνολογία ανασυνδυασμένου DNA. **4. ΚΛΙΝΙΚΕΣ ΠΛΗΡΟΦΟΡΙΕΣ: 4.1 Θεραπευτικές ενδείξεις:** Το YERVOY ενδείκνυται για τη θεραπεία του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία. **4.3 Αντενδείξεις:** Υπερευαισθησία στη δραστική ουσία ή σε κάποιο από τα έκδοχα. **4.4 Ειδικές προειδοποιήσεις και προφυλάξεις κατά τη χρήση:** Το YERVOY σχετίζεται με φλεγμονώδεις ανεπιθύμητες αντιδράσεις που προκύπτουν από αυξημένη ή εκτεταμένη δραστηριότητα του ανοσοποιητικού (ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό) και πιθανόν σχετίζονται με το μηχανισμό δράσης του. Ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό που μπορεί να είναι σοβαρές ή απειλητικές για τη ζωή, είναι πιθανό να συμπεριλαμβάνουν γαστρεντερικές, ηπατικές, δερματικές, νευρολογικές, ενδοκρινολογικές ή άλλων οργανικών συστημάτων. Ενώ οι περισσότερες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό εμφανίστηκαν κατά την περίοδο επαγωγής έχει επίσης αναφερθεί εκδήλωση μήνες μετά από την τελευταία δόση του YERVOY. Εκτός αν προσδιοριστεί διαφορετική αιτιολογία, η διάρροια, η αυξημένη συχνότητα κενώσεων, το αίμα στα κόπρανα, οι αυξήσεις LFT, το έξανθημα και η ενδοκρινοπάθεια πρέπει να θεωρηθούν φλεγμονώδεις και να συνδέονται με το YERVOY. Η πρώιμη διάγνωση και η κατάλληλη διαχείριση είναι απαραίτητες για την ελαχιστοποίηση απειλητικών για τη ζωή επιπλοκών. Συστηματική εισαγωγή υψηλών δόσεων κορτικοστεροειδών με ή χωρίς επιπρόσθετη ανοσοκατασταλτική θεραπεία είναι πιθανό να απαιτηθεί για την αντιμετώπιση σοβαρών ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό. Ειδικές για το YERVOY κατευθυντήριες γραμμές για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό περιγράφονται παρακάτω. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg σε μια μελέτη προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος Φάσης 3 (MDX01020, βλέπε παράγραφο 5.1) ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 35) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, η υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) εμφανίστηκε στις περισσότερες περιπτώσεις (90%) σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Οι ασθενείς πρέπει να παρακολουθούνται για γαστρεντερικά σημεία και συμπτώματα που είναι πιθανό να υποδεικνύουν κολίτιδα σχετιζόμενη με το ανοσοποιητικό ή διάτρηση του γαστρεντερικού σωλήνα. Στην κλινική εικόνα είναι πιθανό να συμπεριλαμβάνεται διάρροια, αυξημένη συχνότητα εντερικών κινήσεων, κοιλιακό άλγος ή αιματοχεσία, με ή χωρίς πυρετό. Διάρροια ή κολίτιδα που εμφανίζεται μετά από την έναρξη του YERVOY πρέπει να αξιολογείται έγκαιρα για τον αποκλεισμό λοιμώδους ή άλλης εναλλακτικής αιτιολογίας. Σε κλινικές δοκιμές, κολίτιδα σχετιζόμενη με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Συστάσεις για την αντιμετώπιση της διάρροιας ή της κολίτιδας βασίζονται στην βαρύτητα των συμπτωμάτων (σύμφωνα με την ταξινόμηση της βαθμολόγησης της βαρύτητας κατά NCICTCAE v3). Ασθενείς με ήπια έως μέτρια (Βαθμού 1 ή 2) διάρροια (αύξηση έως 6 κενώσεις την ημέρα) ή πιθανολογούμενη ήπια έως μέτρια κολίτιδα (π.χ. κοιλιακό άλγος ή αίμα στα κόπρανα), είναι πιθανό να παραμείνουν στο YERVOY. Συνιστάται συμπτωματική θεραπεία (π.χ. λοπεραμίδη, υποκατάσταση υγρών) και προσεκτική παρακολούθηση. Εάν τα ήπια έως μέτρια συμπτώματα υποτροπιάσουν ή επιμείνουν για 57 ημέρες, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλείπεται και θα πρέπει να ξεκινήσει θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg από το στόμα άπαξ ημερησίως ή ισοδύναμο). Εάν παρουσιαστεί υποχώρηση σε Βαθμό 01 ή επιστροφή στην έναρξη, το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) διάρροια ή κολίτιδα (βλέπε παράγραφο 4.2),και πρέπει να ξεκινήσει αμέσως υψηλής δόσης ενδοφλέβια θεραπεία με κορτικοστεροειδή. (Σε κλινικές δοκιμές έχει χρησιμοποιηθεί μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελέγχεται η διάρροια και άλλα συμπτώματα, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται σε κλινική απόφαση. Σε κλινικές δοκιμές, η ταχεία βαθμιαία μείωση και διακοπή (σε διαστήματα < 1 μήνα) οδήγησε στην υποτροπή της διάρροιας ή της κολίτιδας σε ορισμένους ασθενείς. Οι ασθενείς πρέπει να αξιολογούνται για στοιχεία διάτρησης του γαστρεντερικού σωλήνα ή περιτονίτιδας. Η εμπειρία από κλινικές δοκιμές σχετικά με την αντιμετώπιση διάρροιας ανθεκτικής σε κορτικοστεροειδή ή κολίτιδας είναι περιορισμένη. Ωστόσο, είναι δυνατόν να ληφθεί υπόψη η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, προστέθηκε εφάπαξ δόση infliximab 5 mg/kg, εκτός εάν ήταν αντένδειξη. Δεν πρέπει να χρησιμοποιείται infliximab εάν πιθανολογείται διάτρηση του γαστρεντερικού σωλήνα ή σηψαιμία (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για το infliximab). Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 25) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την έναρξη της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Οι ηπατικές τρανσαμινάσες και η χολερυθρίνη πρέπει να αξιολογούνται πριν από κάθε δόση του YERVOY, καθώς πρώιμες εργαστηριακές μεταβολές μπορεί να υποδεικνύουν ανακύπτουσα ηπατίτιδα σχετιζόμενη με το ανοσοποιητικό (βλέπε παράγραφο 4.2). Αυξήσεις σε LFT είναι πιθανό να αναπτυχθούν απουσία κλινικών συμπτωμάτων. Πρέπει να αξιολογούνται αυξήσεις της AST και της ALT ή της ολικής χολερυθρίνης προς αποκλεισμό λοιπών αιτίων κάκωσης του ήπατος, συμπεριλαμβανομένων λοιμώξεων, εξέλιξης της νόσου ή φαρμακευτικών προϊόντων και να παρακολουθούνται έως την υποχώρησή τους. Βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, κατέδειξαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Για ασθενείς με αυξημένη AST ή ALT στο εύρος των > 5-≤ 8 x ULN ή ολική χολερυθρίνη στο εύρος των > 3-≤ 5 x ULN που πιθανολογείται ότι σχετίζεται με το YERVOY, πρέπει να παραλείπεται η προγραμματισμένη δόση του YERVOY και πρέπει να παρακολουθούνται οι LFT έως την υποχώρηση. Όταν βελτιωθούν τα επίπεδα LFT (AST και ALT ≤ 5 x ULN και ολική χολερυθρίνη ≤ 3 x ULN), το YERVOY μπορεί να ξαναρχίσει στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω ανεπιθύμητων αντιδράσεων, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Για ασθενείς με αυξήσεις της AST ή της ALT > 8 x ULN που πιθανολογείται ότι σχετίζονται με το YERVOY, η θεραπεία πρέπει να διακόπτεται οριστικά (βλέπε παράγραφο 4.2) και πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με κορτικοστεροειδή υψηλής δόσης (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg ημερησίως ή ισοδύναμο). Σε αυτούς τους ασθενείς, πρέπει να παρακολουθούνται οι LFT έως την ομαλοποίηση. Όταν υποχωρούν τα συμπτώματα και ομαλοποιηθούν οι αυξήσεις των LFT, η έναρξη βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Αυξήσεις των LFTs κατά τη βαθμιαία μείωση και διακοπή είναι δυνατόν να αντιμετωπιστούν με αύξηση της δόσης του κορτικοστεροειδούς και βραδύτερη βαθμιαία μείωση και διακοπή. Για ασθενείς με σημαντικές αυξήσεις των LFT που είναι ανθεκτικοί σε θεραπεία με κορτικοστεροειδή, είναι δυνατόν να εξεταστεί η προσθήκη ενός εναλλακτικού ανοσοκατασταλτικού παράγοντα στο σχήμα με κορτικοστεροειδή. Σε κλινικές δοκιμές, χρησιμοποιήθηκε μυκοφαινολική μοφετίλη σε ασθενείς χωρίς ανταπόκριση σε θεραπεία με κορτικοστεροειδή ή που παρουσίασαν αύξηση του LFT κατά την βαθμιαία μείωση και διακοπή κορτικοστεροειδών που δεν ανταποκρινόταν σε αύξηση της δόσης των κορτικοστεροειδών (βλέπε την Περίληψη Χαρακτηριστικών του Προϊόντος για τη μυκοφαινολική μοφετίλη). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Εξάνθημα και κνησμός επαγόμενα από YERVOY ήταν κυρίως ήπια ή μέτρια (Βαθμού 1 ή 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 25) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες (εύρος 0,9 έως 16 εβδομάδες) από την έναρξη της θεραπείας. Με ειδικές για το πρωτόκολλο κατευθυντήριες γραμμές για την αντιμετώπιση, παρουσιάστηκε υποχώρηση στις περισσότερες περιπτώσεις (87%), σε διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Εξάνθημα και κνησμός επαγόμενα από YERVOY πρέπει να αντιμετωπίζεται με βάση τη σοβαρότητα. Ασθενείς με μια ήπια έως μέτρια (Βαθμού 1 έως 2) δερματική ανεπιθύμητη αντίδραση μπορούν να παραμείνουν σε θεραπεία με YERVOY με συμπτωματική θεραπεία (π.χ. αντισταμινικά). Για ήπιο έως μέτριο εξάνθημα ή κνησμό που εμμένει για 1 έως 2 εβδομάδες και δεν βελτιώνεται με τοπικά κορτικοστεροειδή, πρέπει να ξεκινήσει η από του στόματος θεραπεία με κορτικοστεροειδή (π.χ. πρεδνιζόνη 1 mg/kg άπαξ ημερησίως ή ισοδύναμο). Για ασθενείς με μια σοβαρή (βαθμού 3) δερματική ανεπιθύμητη αντίδραση, η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί. Εάν βελτιωθούν τα αρχικά συμπτώματα σε ήπια (Βαθμού 1) ή υποχωρήσουν, η θεραπεία με YERVOY μπορεί να συνεχιστεί και πάλι στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης, δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με ένα πολύ σοβαρό (Βαθμού 4) εξάνθημα ή σοβαρό (Βαθμού 3) κνησμό (βλέπε παράγραφο 4.2) και θα πρέπει να ξεκινήσει αμέσως συστηματική ενδοφλέβια θεραπεία με υψηλές δόσεις κορτικοστεροειδών (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Όταν ελεγχθεί το εξάνθημα ή ο κνησμός, η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Το YERVOY σχετίζεται με σοβαρές νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε κλινικές δοκιμές (βλέπε παράγραφο 4.8). Έχουν επίσης αναφερθεί συμπτώματα ομοιάζοντα με μυασθένεια gravis. Οι ασθενείς μπορεί να παρουσιάσουν μυϊκή αδυναμία. Μπορεί ακόμη να παρουσιαστεί αισθητική νευροπάθεια. Ανεξήγητη κινητική νευροπάθεια, μυϊκή αδυναμία ή αισθητική νευροπάθεια που διαρκεί > 4 ημέρες πρέπει να αξιολογείται και θα πρέπει να αποκλειστούν μη φλεγμονώδη αίτια, όπως εξέλιξη της νόσου, λοιμώξεις, μεταβολικά σύνδρομα και φαρμακευτικά προϊόντα. Για ασθενείς με μέτρια (Βαθμού 2) νευροπάθεια (κινητική με ή χωρίς αισθητική) που πιθανόν σχετίζεται με το YERVOY, θα πρέπει να παραλείπεται η προγραμματισμένη δόση. Εάν τα νευρολογικά συμπτώματα υποχωρήσουν στην έναρξη, ο ασθενής μπορεί να ξαναρχίσει το YERVOY στην επόμενη προγραμματισμένη δόση. Δόσεις που παραλείπονται λόγω μιας ανεπιθύμητης αντίδρασης δεν πρέπει να υποκαθίστανται (βλέπε παράγραφο 4.2). Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) αισθητική νευροπάθεια που πιθανολογείται ότι συνδέεται με το YERVOY (βλέπε παράγραφο 4.2). Οι ασθενείς πρέπει να αντιμετωπίζονται σύμφωνα με τις κατευθυντήριες γραμμές του ιδρύματος για την διαχείρηση αισθητικής νευθροπάθειας και πρέπει να ξεκινήσουν αμέσως ενδοφλέβια θεραπεία με κορτικοστεροειδή (π.χ. μεθυλπρεδνιζολόνη 2 mg/kg/ημέρα). Προοδευτικά σημάδια κινητικής νευροπάθειας θα πρέπει να θεωρείται ότι σχετίζονται με το ανοσοποιητικό και να αντιμετωπίζονται ανάλογα. Το YERVOY πρέπει να διακόπτεται οριστικά σε ασθενείς με σοβαρή (Βαθμού 3 ή 4) κινητική νευροπάθεια ανεξαρτήτως αιτιολογίας (βλέπε παράγραφο 4.2). Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό: Το YERVOY μπορεί να προκαλέσει φλεγμονή των οργάνων του ενδοκρινικού συστήματος, συγκεκριμένα υποφυσίτιδα, υποϋποφυσισμό, επινεφριδιακή ανεπάρκεια και υποθυρεοειδισμό και οι ασθενείς μπορεί να παρουσιάσουν μη ειδικά συμπτώματα, τα οποία μπορεί να μοιάζουν με άλλα αίτια, όπως μετάσταση στον εγκέφαλο ή υποκείμενη νόσο. Στη συχνότερη κλινική εικόνα συμπεριλαμβάνεται η κεφαλαλγία και η κόπωση. Στα συμπτώματα μπορεί να συμπεριλαμβάνονται ελλείμματα του οπτικού πεδίου, αλλαγές της συμπεριφοράς, διαταραχές των ηλεκτρολυτών και υπόταση. Επινεφριδιακή κρίση ως αίτιο των συμπτωμάτων του ασθενούς πρέπει να αποκλείεται. Η κλινική εμπειρία με ενδοκρινοπάθεια σχετιζόμενη με το YERVOY είναι περιορισμένη. Για ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 24) ενδοκρινοπάθειας σχετιζόμενης με το ανοσοποιητικό κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την έναρξη της θεραπείας. Ενδοκρινοπάθεια που συνδέεται με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με ανοσοκατασταλτική θεραπεία και θεραπεία υποκατάστασης ορμονών. Εάν υπάρχουν οποιαδήποτε σημεία επινεφριδιακής κρίσης, όπως σοβαρή αφυδάτωση, υπόταση ή καταπληξία, συνιστάται άμεση χορήγηση ενδοφλέβιων κορτικοστεροειδών με αλατοκορτικοειδική δράση και ο ασθενής θα πρέπει να αξιολογηθεί για την παρουσία σηψαιμίας ή λοιμώξεων. Εάν υπάρχουν σημεία επινεφριδιακής ανεπάρκειας, αλλά ο ασθενής δεν βρίσκεται σε επινεφριδιακή κρίση, πρέπει να εξεταστούν περαιτέρω παρακλινικές εξετάσεις στις οποίες συμπεριλαμβάνεται η αξιολόγηση εργαστηριακών και απεικονιστικών ελέγχων. Η αξιολόγηση των αποτελεσμάτων των εργαστηριακών ελέγχων για την έλεγχο της ενδοκρινούς λειτουργίας πρέπει να πραγματοποιείται πριν από την έναρξη θεραπείας με κορτικοστεροειδή. Εάν οι απεικονιστικοί έλεγχοι της υπόφυσης ή εργαστηριακοί έλεγχοι της ενδοκρινούς λειτουργίας είναι μη φυσιολογικοί, συνιστάται βραχύ σχήμα θεραπείας με υψηλές δόσεις κορτικοστεροειδών (π.χ. δεξαμεθαζόνη 4 mg ανά 6 ώρες ή ισοδύναμο) ώστε να αντιμετωπιστεί η φλεγμονή του προσβεβλημένου αδένα και η προγραμματισμένη δόση του YERVOY θα πρέπει να παραλειφθεί (βλέπε παράγραφο 4.2). Αυτή τη στιγμή είναι άγνωστο εάν η θεραπεία με κορτικοστεροειδή αναστρέφει την αδενική δυσλειτουργία. Θα πρέπει επίσης να ξεκινήσει κατάλληλη υποκατάσταση ορμονών. Είναι πιθανό να είναι απαραίτητη μακροχρόνια θεραπεία με υποκατάσταση ορμονών. Όταν τεθούν υπό έλεγχο τα συμπτώματα ή οι μη φυσιολογικές εργαστηριακές τιμές και είναι εμφανής η βελτίωση του ασθενούς συνολικά, μπορεί να συνεχιστεί η θεραπεία με YERVOY και η έναρξη της βαθμιαίας μείωσης και διακοπής των κορτικοστεροειδών πρέπει να βασίζεται στην κλινική απόφαση. Η βαθμιαία μείωση και διακοπή πρέπει να γίνεται μέσα σε διάστημα τουλάχιστον 1 μήνα. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό: Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν πεπτιδικό εμβόλιο με YERVOY 3 mg/kg + gp100 στην MDX01020 (βλέπε παράγραφο 4.8). Αν οι αντιδράσεις είναι σοβαρές (Βαθμού 3 ή 4) είναι πιθανό να απαιτηθεί άμεσα θεραπεία με υψηλές δόσεις κορτικοστεροειδών και διακοπή του YERVOY (βλέπε παράγραφο 4.2). Για ραγοειδίτιδα, ιρίτιδα ή επισκληρίτιδα που συνδέεται με το YERVOY, θα πρέπει να εξετάζεται η χρήση τοπικών κορτικοστεροειδών στη μορφή των οφθαλμικών σταγόνων όπως ενδείκνυται ιατρικά. Ειδικοί πληθυσμοί: Ασθενείς με οφθαλμικό μελάνωμα, πρωτοπαθές μελάνωμα του ΚΝΣ και ενεργές μεταστάσεις του εγκεφάλου δεν συμπεριελήφθησαν στην πιλοτική κλινική δοκιμή (βλέπε παράγραφο 5.1). Αντίδραση στην έγχυση: Υπήρχαν μεμονωμένες αναφορές σοβαρών αντιδράσεων στην έγχυση σε κλινικές δοκιμές. Σε περίπτωση σοβαρής αντίδρασης στην έγχυση, η έγχυση YERVOY πρέπει να διακόπτεται και να χορηγείται κατάλληλη ιατρική θεραπεία. Ασθενείς με ήπια ή μέτρια αντίδραση στην έγχυση, μπορούν να λάβουν YERVOY με προσεκτική παρακολούθηση. Μπορεί να ληφθεί υπόψη η προφαρμακευτική αγωγή με αντιπυρετικό και αντισταμινικό. Ασθενείς με αυτοάνοση νόσο: Ασθενείς με ιστορικό αυτοάνοσης νόσου (εκτός από λεύκη και επαρκώς ελεγχόμενη ανεπάρκεια ενδοκρίνης, όπως υποθυρεοειδισμός), συμπεριλαμβανομένων αυτών για τους οποίους απαιτείται συστηματική ανοσοκατασταλτική θεραπεία για προϋπάρχουσα ενεργό αυτοάνοση νόσο ή για διατήρηση μοσχεύματος μετά από μεταμόσχευση οργάνου, δεν αξιολογήθηκαν σε κλινικές δοκιμές. Το ipilimumab είναι ενισχυτής των Τκυττάρων που καθιστά δυνατή την ανοσολογική ανταπόκριση (βλέπε παράγραφο 5.1) και είναι πιθανό να παρέμβει στην ανοσοκατασταλτική θεραπεία, γεγονός που οδηγεί σε παροξυσμό της υποκείμενης νόσου ή αυξημένο κίνδυνο απόρριψης του μοσχεύματος. Το YERVOY πρέπει να αποφεύγεται σε ασθενείς με σοβαρή ενεργό αυτοάνοση νόσο, σε περιπτώσεις στις οποίες περαιτέρω ενεργοποίηση του ανοσοποιητικού είναι ενδεχομένως άμεσα απειλητική για τη ζωή και χρησιμοποιείται με προσοχή σε άλλους ασθενείς με ιστορικό αυτοάνοσης νόσου, μετά από προσεκτική εξέταση του ενδεχόμενου κινδύνου-οφέλους σε ατομική βάση. Ασθενείς που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. Κάθε ml αυτού του φαρμακευτικού προϊόντος περιέχει 0,1 mmol (ή 2,30 mg) νατρίου. Θα πρέπει να λαμβάνεται υπόψη κατά την θεραπεία ασθενών που ακολουθούν δίαιτα με ελεγχόμενη περιεκτικότητα σε νάτριο. **4.8 Ανεπιθύμητες ενέργειες: Περίληψη του προφίλ ασφάλειας:** Το YERVOY έχει χορηγηθεί σε > 3.000 ασθενείς σε ένα κλινικό πρόγραμμα το οποίο αξιολόγησε τη χρήση του με διάφορες δόσεις και τύπους όγκων. Εκτός εάν ορίζεται διαφορετικά, τα δεδομένα παρακάτω αποτυπώνουν την έκθεση σε YERVOY στα 3 mg/kg σε κλινικές δοκιμές μελανώματος. Στη μελέτη Φάσης 3 MDX01020, (βλέπε παράγραφο 5.1), οι ασθενείς έλαβαν ένα διάμεσο 4 δόσεων (εύρος 14). Το YERVOY σχετίζεται πολύ συχνά με ανεπιθύμητες ενέργειες που προκύπτουν από αυξημένη ή εντεταμένη δράση του ανοσοποιητικού. Οι περισσότερες από αυτές, στις οποίες συμπεριλαμβάνονται σοβαρές αντιδράσεις, υποχώρησαν μετά από την έναρξη κατάλληλης ιατρικής θεραπείας ή τη διακοπή του YERVOY (βλέπε παράγραφο 4.4 για την αντιμετώπιση ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό). Σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg στην MDX01020, οι ανεπιθύμητες ενέργειες που αναφέρθηκαν συχνότερα (≥ 10% των ασθενών), ήταν διάρροια, εξάνθημα, κνησμός, κόπωση, ναυτία, έμετος, μειωμένη όρεξη και κοιλιακό άλγος. Στην πλειονότητά τους ήταν ήπιες έως μέτριες (Βαθμού 1 ή 2). Η θεραπεία με YERVOY διακόπηκε λόγω ανεπιθύμητων ενεργειών στο 10% των ασθενών. Κατάλογος ανεπιθύμητων ενεργειών σε πίνακα: Ανεπιθύμητες ενέργειες που αναφέρθηκαν σε ασθενείς με προχωρημένο μελάνωμα, οι οποίοι έλαβαν YERVOY 3 mg/kg σε κλινικές δοκιμές (n = 767), παρουσιάζονται στον Πίνακα 2. Αυτές οι αντιδράσεις παρουσιάζονται ανά κατηγορία συστήματος οργάνων σύμφωνα με την συχνότητα. Η συχνότητα ορίζεται ως εξής: πολύ συχνές (≥ 1/10), συχνές (≥ 1/100 έως < 1/10), όχι συχνές (≥ 1/1.000 έως < 1/100), σπάνιες (≥ 1/10.000 έως < 1/1.000), πολύ σπάνιες (< 1/10.000). Εντός κάθε κατηγορίας συχνότητας εμφάνισης, οι ανεπιθύμητες ενέργειες εμφανίζονται κατά φθίνουσα σειρά σοβαρότητας. Τα ποσοστά ανεπιθύμητων αντιδράσεων που συνδέονται με το ανοσοποιητικό σε HLAA2*0201 θετικούς ασθενείς οι οποίοι έλαβαν YERVOY στην MDX01020, ήταν παρόμοια με εκείνα που παρατηρήθηκαν στο κλινικό πρόγραμμα συνολικά.

Πίνακας 2: Ανεπιθύμητες ενέργειες σε ασθενείς με προχωρημένο μελάνωμα που έλαβαν YERVOY 3 mg/kg (n = 767)[α]	
Λοιμώξεις και παρασιτώσεις	
Όχι συχνές	σηψαιμία[β], σηπτική καταπληξία[β], μηνιγγίτιδα, γαστρεντερίτιδα, εκκολπωματίτιδα, ουρολοίμωξη, λοίμωξη του ανώτερου αναπνευστικού συστήματος, λοίμωξη του κατώτερου αναπνευστικού συστήματος
Νεοπλάσματα καλοήθη, κακοήθη και μη καθορισμένα (περιλαμβάνονται κύστεις και πολύποδες)	
Συχνές	πόνος από όγκο
Όχι συχνές	παρανεοπλασματικό σύνδρομο
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	
Συχνές	αναιμία, λεμφοπενία
Όχι συχνές	αιμολυτική αναιμία[β], θρομβοπενία, ηωσινοφιλία, ουδετεροπενία
Διαταραχές του ανοσοποιητικού συστήματος	
Όχι συχνές	υπερευαισθησία
Διαταραχές του ενδοκρινικού συστήματος	
Συχνές	υποϋποφυσισμός (συμπεριλαμβάνεται η υποφυσίτιδα)[γ], υποθυρεοειδισμός[γ]
Όχι συχνές	επινεφριδιακή ανεπάρκεια[γ], υπερθυρεοειδισμός[γ], υπογοναδισμός
Διαταραχές του μεταβολισμού και της θρέψης	
Πολύ συχνές	μειωμένη όρεξη
Συχνές	αφυδάτωση, υποκαλιαιμία
Όχι συχνές	υπονατριαιμία, αλκάλωση, υποφωσφοραιμία, σύνδρομο λύσης όγκου
Ψυχιατρικές διαταραχές	
Συχνές	συγχυτική κατάσταση
Όχι συχνές	μεταβολές της νοητικής κατάστασης, κατάθλιψη, μειωμένη γενετήσια ορμή
Διαταραχές του νευρικού συστήματος	
Συχνές	περιφερική αισθητική νευροπάθεια, ζάλη, κεφαλαλγία, λήθαργος
Όχι συχνές	σύνδρομο Guillain-Barré[β,γ], συγκοπή, κρανιακή νευροπάθεια, εγκεφαλικό οίδημα, περιφερική νευροπάθεια, αταξία, τρόμος, μυόκλωνος, δυσαρθρία
Οφθαλμικές διαταραχές	
Συχνές	θαμπή όραση, πόνος του οφθαλμού
Όχι συχνές	ραγοειδίτιδα[γ], αιμορραγία του υαλοειδούς σώματος, ιρίτιδα[γ], μειωμένη οπτική οξύτητα, αίσθημα ξένου σώματος στους οφθαλμούς, επιπεφυκίτιδα
Καρδιακές διαταραχές	
Όχι συχνές	αρρυθμία, κολπική μαρμαρυγή
Αγγειακές διαταραχές	
Συχνές	υπόταση, έξαψη
Όχι συχνές	αγγειίτιδα, αγγειοπάθεια[β], περιφερική ισχαιμία, ορθοστατική υπόταση
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	
Συχνές	δύσπνοια, βήχας
Όχι συχνές	αναπνευστική ανεπάρκεια, σύνδρομο οξείας αναπνευστικής δυσχέρειας[β], διήθηση πνεύμονα, πνευμονικό οίδημα, πνευμονίτιδα, αλλεργική ρινίτιδα
Διαταραχές του γαστρεντερικού	
Πολύ συχνές	διάρροια[γ], έμετος, ναυτία
Συχνές	γαστρεντερική αιμορραγία, κολίτιδα[β,γ], δυσκοιλιότητα, γαστροοισοφαγική παλινδρόμηση, κοιλιακό άλγος
Όχι συχνές	διάτρηση του γαστρεντερικού σωλήνα[β,γ], διάτρηση του παχέος εντέρου[β,γ], διάτρηση του εντέρου[β,γ], περιτονίτιδα[β], παγκρεατίτιδα, εντεροκολίτιδα, γαστρικό έλκος, έλκος του παχέος εντέρου, οισοφαγίτιδα, ειλεός[δ]
Διαταραχές του ήπατος και των χοληφόρων	
Συχνές	μη φυσιολογική ηπατική λειτουργία
Όχι συχνές	ηπατική ανεπάρκεια[β,γ], ηπατίτιδα, ηπατομεγαλία, ίκτερος
Διαταραχές του δέρματος και του υποδόριου ιστού	
Πολύ συχνές	εξάνθημα[γ], κνησμός[γ]
Συχνές	δερματίτιδα, ερύθημα, λεύκη, κνίδωση, αλωπεκία, νυκτερινοί ιδρώτες, ξηροδερμία
Όχι συχνές	τοξική επιδερμική νεκρόλυση[β,γ], λευκοκυτταροκλαστική αγγειίτιδα, αποφολίδωση δέρματος
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	
Συχνές	αρθραλγία, μυαλγία, μυοσκελετικός πόνος, μυϊκοί σπασμοί
Όχι συχνές	ρευματική πολυμυαλγία, αρθρίτιδα-
Διαταραχές των νεφρών και των ουροφόρων οδών	
Όχι συχνές	νεφρική ανεπάρκεια[β], σπειραματονεφρίτιδα[γ], νεφρική σωληναριακή οξέωση
Διαταραχές του αναπαραγωγικού συστήματος και του μαστού	
Όχι συχνές	αμηνόρροια
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	
Πολύ συχνές	κόπωση, αντίδραση της θέσης ένεσης, πυρεξία
Συχνές	ρίγη, εξασθένιση, οίδημα, άλγος
Όχι συχνές	πολυοργανική ανεπάρκεια[β,γ], σχετιζόμενη με την έγχυση αντίδραση
Παρακλινικές εξετάσεις	
Συχνές	αυξημένη αμινοτρανσφεράση της αλανίνης[γ], αυξημένη ασπαρτική αμινοτρανσφεράση[γ], αυξημένη χολερυθρίνη αίματος, μειωμένο σωματικό βάρος
Όχι συχνές	μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας, αυξημένη κρεατινίνη αίματος, αυξημένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη κορτιζόλη αίματος, μειωμένη κορτικοτροφίνη αίματος, αυξημένη λιπάση[γ], αυξημένη αμυλάση αίματος[γ], μειωμένη τεστοστερόνη αίματος

α Οι συχνότητες βασίζονται σε συγκεντρωτικά στοιχεία από 9 κλινικές δοκιμές που εξέτασαν το YERVOY 3 mg/kg δόση σε μελάνωμα.

β Συμπεριλαμβάνεται η θανατηφόρος έκβαση.

γ Πρόσθετες πληροφορίες σχετικά με αυτές τις πιθανώς φλεγμονώδεις ανεπιθύμητες ενέργειες παρέχονται στην «Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών» και την παράγραφο 4.4. Τα δεδομένα που παρουσιάζονται σε αυτές τις παραγράφους αποτυπώνουν κυρίως την εμπειρία από μια μελέτη Φάσης 3, την MDX01020.

δ Αναφέρονται σε πρόσφατες μελέτες εκτός των ολοκληρωμένων κλινικών δοκιμών στο μελάνωμα.

Πρόσθετες ανεπιθύμητες ενέργειες που δεν αναφέρονται στον Πίνακα 2 έχουν αναφερθεί σε ασθενείς που έλαβαν άλλες δόσεις (είτε < ή > 3 mg/kg) YERVOY σε κλινικές δοκιμές μελανώματος. Αυτές οι πρόσθετες αντιδράσεις παρουσιάστηκαν όλες σε συχνότητα < 1%: μηνιγγισμός, μυοκαρδίτιδα, καρδιομυοπάθεια, αυτοάνοση ηπατίτιδα, πολύμορφο ερύθημα, αυτοάνοση νεφρίτιδα, συμπτώματα ομοιάζοντα με μυασθένεια gravis, αυτοάνοση θυρεοειδίτιδα, υπερυποφυσισμός, δευτεροπαθής ανεπάρκεια του φλοιού των επινεφριδίων, υποπαραθυρεοειδισμός, θυρεοειδίτιδα, επισκληρίτιδα, βλεφαρίτιδα, οίδημα του οφθαλμού, σκληρίτιδα, κροταφική αρτηρίτιδα, φαινόμενο Raynaud, πρωκτίτιδα, σύνδρομο παλαμοπελματιαίας ερυθροδυσαισθησίας, ψωρίαση, αιματουρία, πρωτεϊνουρία, μειωμένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη γοναδοτροφίνη αίματος, μειωμένη θυροξίνη, λευκοπενία και πολυκυτταραιμία. Περιγραφή επιλεγμένων ανεπιθύμητων ενεργειών: Με εξαίρεση τις περιπτώσεις στις οποίες επισημαίνεται, τα δεδομένα για τις παρακάτω επιλεγμένες ανεπιθύμητες ενέργειες βασίζονται σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg (n = 131) ή YERVOY 3 mg/kg σε συνδυασμό με gp100 (n = 380) σε μια μελέτη Φάσης 3 του προχωρημένου (μη χειρουργήσιμου ή μεταστατικού) μελανώματος (MDX01020, βλέπε παράγραφο 5.1). Οι κατευθυντήριες γραμμές για την αντιμετώπιση αυτών των ανεπιθύμητων ενεργειών περιγράφονται στην παράγραφο 4.4. Γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρα περιστατικά λόγω διάτρησης του γαστρεντερικού σωλήνα έχουν αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με gp100. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε διάρροια και κολίτιδα οποιασδήποτε βαρύτητας στο 27% και το 8% αντίστοιχα. Η συχνότητα σοβαρής (Βαθμού 3 ή 4) διάρροιας και σοβαρής (Βαθμού 3 ή 4) κολίτιδας ήταν 5% για το καθένα. Ο διάμεσος χρόνος έως την εκδήλωση σοβαρών ή θανατηφόρων (Βαθμού 3 έως 5) γαστρεντερικών αντιδράσεων που συνδέονται με το ανοσοποιητικό ήταν 8 εβδομάδες (εύρος 5 έως 13 εβδομάδες) από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο η υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (90%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση (ορίζεται ως βελτίωση σε ήπια [Βαθμού 1] ή λιγότερο ή στη σοβαρότητα κατά την έναρξη) 4 εβδομάδες (εύρος 0,6 έως 22 εβδομάδες). Σε κλινικές δοκιμές η κολίτιδα που συνδέεται με το ανοσοποιητικό συσχετίστηκε με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξελκώσεις και λεμφοκυτταρική και ουδετεροφιλική διήθηση. Ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρή ηπατοτοξικότητα που συνδέεται με το ανοσοποιητικό. Θανατηφόρος ηπατική ανεπάρκεια έχει αναφερθεί σε < 1% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg. Αυξήσεις της AST και της ALT οποιασδήποτε βαρύτητας αναφέρθηκαν στο 1% και το 2% των ασθενών αντίστοιχα. Δεν υπήρχαν αναφορές σοβαρής (Βαθμού 3 ή 4) αύξησης της AST ή της ALT. Ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανατηφόρου (Βαθμού 2 έως 5) ηπατοτοξικότητας που συνδέεται με το ανοσοποιητικό κυμάνθηκε από 3 έως 9 εβδομάδες από την αρχή της θεραπείας. Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμάνθηκε από 0,7 έως 2 εβδομάδες. Σε κλινικές δοκιμές, βιοψίες ήπατος από ασθενείς που είχαν ηπατοτοξικότητα σχετιζόμενη με το ανοσοποιητικό, εμφάνισαν στοιχεία οξείας φλεγμονής (ουδετερόφιλα, λεμφοκύτταρα και μακροφάγα). Δερματικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντιδράσεις που μπορεί να συνδέονται με το ανοσοποιητικό. Θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY σε συνδυασμό με gp100 (βλέπε παράγραφο 5.1). Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε εξάνθημα και κνησμός διαφορετικής βαρύτητας, το καθένα στο 27% των ασθενών. Εξάνθημα και κνησμός επαγόμενο από YERVOY ήταν κυρίως ήπια (Βαθμού 1) ή μέτρια (Βαθμού 2) και ανταποκρίνονταν σε συμπτωματική θεραπεία. Ο διάμεσος χρόνος έως την εκδήλωση μέτριων έως σοβαρών ή θανατηφόρων (Βαθμού 2 έως 5) δερματικών ανεπιθύμητων αντιδράσεων ήταν 3 εβδομάδες από την αρχή της θεραπείας (εύρος 0,9 έως 16 εβδομάδες). Με κατευθυντήριες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, υποχώρηση παρουσιάστηκε στις περισσότερες περιπτώσεις (87%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (εύρος 0,6 έως 29 εβδομάδες). Νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Το YERVOY σχετίζεται με σοβαρές νευρολογικές ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Θανατηφόρο σύνδρομο Guillain-Barré έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με gp100. Συμπτώματα ομοιάζοντα με μυασθένεια gravis έχουν επίσης αναφερθεί σε < 1% των ασθενών που έλαβαν υψηλότερες δόσεις YERVOY σε κλινικές δοκιμές. Ενδοκρινοπάθεια που συνδέονται με το ανοσοποιητικό. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, υποϋποφυσισμός οποιασδήποτε βαρύτητας αναφέρθηκε στο 4% των ασθενών. Επινεφριδιακή ανεπάρκεια, υπερθυρεοειδισμός και υποθυρεοειδισμός οποιασδήποτε βαρύτητας αναφέρθηκε το καθένα στο 2% των ασθενών. Η συχνότητα σοβαρού (Βαθμού 3 ή 4) υποϋποφυσισμού αναφέρθηκε στο 3% των ασθενών. Δεν υπήρχαν αναφορές σοβαρής ή πολύ σοβαρής (Βαθμού 3 ή 4) επινεφριδιακής ανεπάρκειας, υπερθυρεοειδισμού ή υποθυρεοειδισμού. Ο χρόνος έως την εκδήλωση μέτριας έως πολύ σοβαρής (Βαθμού 2 έως 4) σχετιζόμενης με το ανοσοποιητικό ενδοκρινοπάθειας κυμάνθηκε από 7 έως περίπου 20 εβδομάδες από την αρχή της θεραπείας. Ενδοκρινοπάθεια σχετιζόμενη με το ανοσοποιητικό που παρατηρήθηκε σε κλινικές δοκιμές, ήταν γενικώς ελεγχόμενη με θεραπεία υποκατάστασης ορμονών. Άλλες ανεπιθύμητες αντιδράσεις που συνδέονται με το ανοσοποιητικό. Οι παρακάτω ανεπιθύμητες αντιδράσεις που πιθανολογείται ότι συνδέονται με το ανοσοποιητικό, έχουν αναφερθεί σε < 2% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg: ραγοειδίτιδα, ηωσινοφιλία, αύξηση λιπάσης και σπειραματονεφρίτιδα. Επιπροσθέτως, ιρίτιδα, αιμολυτική αναιμία, αυξήσεις αμυλάσης, πολυοργανική ανεπάρκεια και πνευμονίτιδα έχουν αναφερθεί σε ασθενείς που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με πεπτιδικό εμβόλιο gp100. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυάλινο) x 10 ml με ενδεικτική Νοσοκομειακή τιμή 3.887,16 €, και ενδεικτική Χονδρική τιμή τιμή 4.468,00 €. YERVOY 5 mg/ml πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση – Συσκευασία: 1 Φιαλίδιο (γυάλινο) x 40 ml με ενδεικτική Νοσοκομειακή τιμή 15.548,65 €, και ενδεικτική Χονδρική τιμή τιμή 17.872,01 €.

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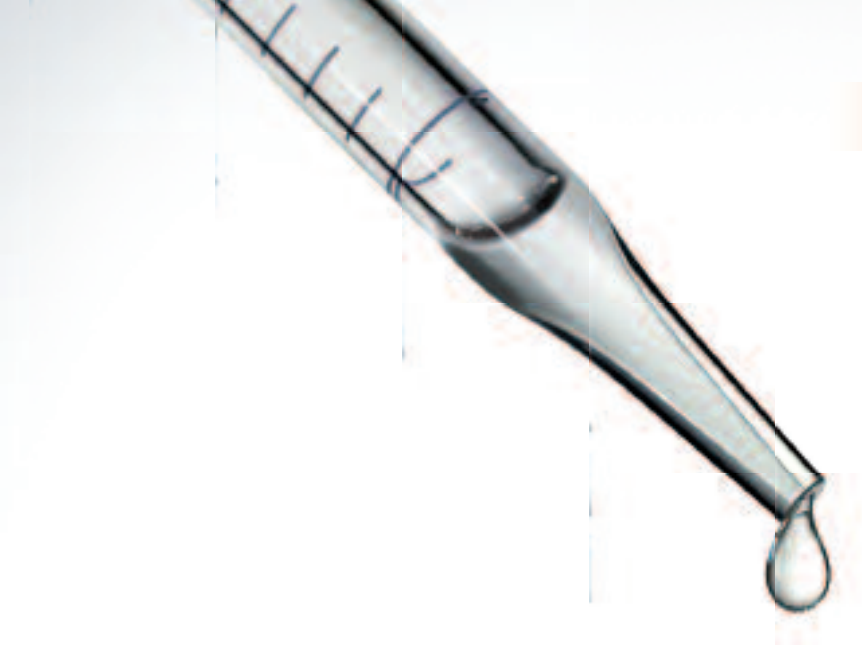

ΚΑΙ ΤΩΡΑ ΕΓΚΕΚΡΙΜΕΝΟ

Το YERVOY™ (ipilimumab) ενδείκνυται για τη θεραπεία του προχωρημένου (ανεγχείρητου ή μεταστατικού) μελανώματος σε ενηλίκους που έχουν λάβει προηγούμενη θεραπεία.[1]

ΠΡΟΟΔΟΣ ΤΗΣ ΕΠΙΣΤΗΜΗΣ
ΣΤΟ ΜΕΤΑΣΤΑΤΙΚΟ ΜΕΛΑΝΩΜΑ

Η δύναμη του ανοσοποιητικού συστήματος

Η σπουδαιότητα της παρατεταμένης επιβίωσης

- **YERVOY™: Ο πρώτος εγκεκριμένος παράγοντας που παρατείνει σημαντικά τη συνολική επιβίωση σε ασθενείς με προχωρημένο μελάνωμα*[2]**
- **YERVOY™: Μια νέα θεραπεία ενίσχυσης των Τ-κυττάρων που ενεργοποιεί το ανοσοποιητικό σύστημα ώστε αυτό να καταστρέφει τους καρκινικούς όγκους.[1]**

Για σημαντικές πληροφορίες ασφάλειας, ανατρέξτε στην Περίληψη Χαρακτηριστικών Προϊόντος του YERVOY™

Bristol-Myers Squibb

YERVOY™ (ipilimumab)
πυκνό διάλυμα για παρασκευή διαλύματος προς έγχυση

*Σε μια τυχαιοποιημένη, ελεγχόμενη δοκιμή φάσης 3.

1. Περίληψη Χαρακτηριστικών Προϊόντος του YERVOY™. 2. Hodi FS *et al. N Engl J Med.* 2010;363(8):711-723.