

FORUM of CLINICAL ONCOLOGY

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the field of oncology**

**Abbreviated course of
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**Recent developments in
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**Metastatic renal cell cancer: what is the sequential treatment
for long-term clinical benefit?**

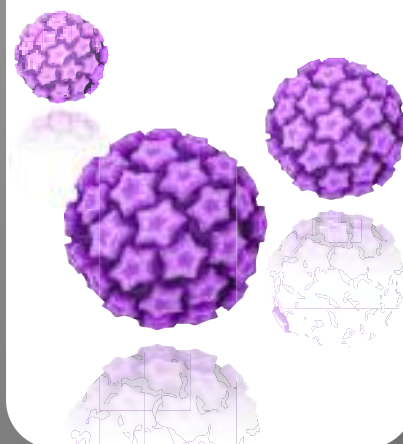
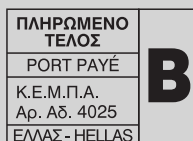
**Adrenal incidentalomas in cancer patients
are not always “innocent”**



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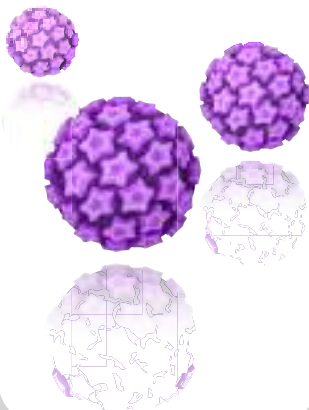
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Medical malpractice redefined

Editorial

Vassilios Barbounis

In the series of invited contributions on topics pertaining to the broader notions of practicing medicine; ethics; economy; oncology as a form of art; good clinical practice; and research -to name but a few without covering the entire list- the current issue hosts an outstanding article [FCO 2013 Mar; 4(1):9-25] on medical malpractice.

The article in question contains an exhaustive analysis of all aspects of this very important subject that is likely to be dealt with by most -if not all- doctors at some point in their careers.

Medical malpractice is a social dimension of modern medicine that concerns citizens, healthcare professionals, insurance and welfare agencies, the justice system and the state. The mere fact that most claims are dropped, withdrawn or dismissed does not moderate the issue's substance.

The author refers extensively to the importance of cost, alluding to the increase of civil liability premiums for healthcare professionals, as well as to the tremendous escalation of healthcare provision costs -a question of great concern in these times of financial crisis.

He distinguishes among the various types and degrees of medical malpractice and makes particular notice of the pharmaceutical industry and/or government agency responsibilities.

It goes without saying that this phenomenon acquires momentous significance within the context of oncology, with emphasis on experimental treatments and the debate on the promotion of research and science being tempered by safety and the avoidance of doing harm. The importance of informed consent prior to therapy is also highlighted.

Defensive medicine practices take up a key place in the article, along with the social and financial cost they entail, as well as the wholesome practice of medicine with a concomitant service quality assurance.

Last but not least, the author suggests recommendations aimed at helping avoid unpleasant situations and contribute to the improvement of patient-physician relations; but mainly they improve the level of service -which, in the final analysis, is the ultimate goal.

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Medical malpractice in the field of oncology

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ABSTRACT

Once an Oncologist or other Health Care Professional (HCP) agrees to treat a patient, he/she has a professional duty to provide competent care. A patient who believes that he/she has received improper medical treatment may be entitled to take legal action against those who administered that treatment. Typically, all persons, institutions and organizational entities involved with the treatment are named as defendants.

This work reviews and comments all types of lawsuits following malpractice (simple negligence, gross negligence and deliberated torts) and product liability; the elements legally required by the plaintiff to prove malpractice and by the defendant to prove innocence and furthermore the profile of the "Reasonable Health Care Professional". Moreover, it presents the potential areas of litigation, characteristic examples of lawsuits, legal defenses to liability and "scientific arms" to avoid litigation for Oncologist Experts.

Key words: medical malpractice; negligence; reasonable man; injury; damage.

INTRODUCTION

Once a Physician or other HCP agrees to treat a patient, he/she has a professional duty to provide competent care. In Oncology, patients should receive the best cancer diagnosis, treatment and care; there should be a freedom from accidental injury due to medical care or errors; and absence of misuse of services. In the medical malpractice context, liability emanates from the HCP's failure to conform to the profession's customary practice. The plaintiff must show some actual, compensable injury that is the result of the alleged negligent care. Proof of injury can include the physical effects of the treatment, but it can also include emotional effects [7, 8, 19]. Conversely, if the defendant doctor adheres to customary practice, he/she cannot be found to have committed malpractice.

The Reasonable Health Care Professional (R-HCP)

A hypothetical person who exercises those qualities which society requires of its members for the protection of their own interest and the interests of others. In law, the reasonable person is not an average or typical person but a composite of the community's judgment as to how the typical community member should behave in situations that might pose a threat of harm to the public.

In medicine, it provides an objective by which the conduct of HCPs is judged. The law considers a variety of factors in determining whether an HCP has acted as the hypothetical reasonable specialist would have acted in a similar situation. These factors include [7, 17, 18]:

An HCP

Knowledge, experience,
and perception

- must take into account actual knowledge or lack of knowledge of various situations (therapies and/or diagnostic procedures) as an R-HCP always does.

Special skills

- cannot deny personal scientific knowledge.
- If an HCP engages in a medical procedure requiring special skills, education, training, or experience, the standard by which his/her conduct is measured is the conduct of a reasonably skilled, competent, and experienced HCP who is a qualified member of the group authorized to engage in that activity.

	<ul style="list-style-type: none">■ The law does not make a particular allowance for a resident/ trainee/ beginner/ experienced health scientist with regard to special skills. He/She is held to the standard of conduct of HCPs who are reasonably skilled and experienced in the activity.
Physical characteristics	The law takes an HCP's physical characteristics into account in determining whether that person's conduct is negligent. A physically impaired individual cannot be expected to conform to a standard of conduct that would be physically impossible for him/her to meet.
Mental capacity	<ul style="list-style-type: none">■ Lack of intelligence, judgment, memory, or emotional stability does not excuse the HCP's failure to act as a reasonably prudent HCP would have acted under the same circumstances.■ Generally, the courts consider that, members of the public are unable to identify an HCP (and moreover a medical doctor) with a mental illness. Consequently, to protect the public, the courts do not accept mental illness as a bar to recovery for a liable third party.
Emergencies	<ul style="list-style-type: none">■ An HCP's conduct in an emergency is evaluated in light of whether it was a reasonable response under the circumstances, even though another course of action might have avoided the injury.■ In some circumstances, failure to anticipate an emergency may constitute negligence. The R-HCP anticipates, and takes precautions against, foreseeable emergencies.■ An HCP can be negligent in causing an emergency, even if he/she acts reasonably during the emergency.
Conduct of others	An R-HCP <ul style="list-style-type: none">■ takes into account the conduct of others and regulates his/her own conduct accordingly.■ must even foresee the unlawful or negligent conduct of others if the situation warrants it.

Special attention must be paid to ionizing radiation. Along with surgery and chemotherapy, radiation therapy is one of the most important methods of cancer treatment. Almost all specialists in the medical use of radiation (e.g., Radiation Oncologists, Physicists, Biologists, Radiologists) are convinced that the magnitude of the public's fear is unreasonable. The law, however, properly recognizes a cause of action in tort for radiation injury [20].

A patient who believes that he or she has received improper medical treatment may be entitled to take legal action against those who administrated that treatment. Typically, all persons, institutions and organizational entities involved with the treatment are named as defendants.

Volume of malpractice cases. Brennan and his colleagues [21] reviewed 30,121 randomly selected records. They found that 3.7% of all hospitalized patients experienced an adverse event (defined as injury caused by medical management). Belk [22] found that 16,682 claims for medical malpractice have been registered in the USA in 2001. Medical errors are the leading cause of accidental death in the US, where 44,000-98,000 persons die from medical errors annually (1997 estimates) [23, 24]. Medical errors are also the cause of preventable harm and related adverse events related in 10% of patients in hospitals in Europe; 16.6% of Australian hospital patients; 7.5% of patients admitted to Canadian hospitals and 12.9% of public hospital admissions in New Zealand [8]. In Oncology, medical errors have been reported between 1.5-11.0% of chemotherapeutic prescriptions [25] or over- or underdosing radiotherapy leading to increased death.

Doctors facing a malpractice claim. 7.4% of all Physicians

experienced a malpractice suit from 1991 to 2005 [26] in the USA. It is expected that 75% of Physicians in "low-risk" specialties and virtually 100% of Physicians in "high-risk" specialties could face a malpractice claim during their careers [26, 27]. These claims are categorized as follows: "High-risk" specialties for claim/year: Neurosurgery (19.1%); Thoracic-Cardiovascular Surgery (18.9%); General Surgery (15.3%); Orthopedic Surgery (14.8%); Plastic Surgery (13%); Obstetrics and Gynecology (12%); Urology (10.5%). "Low-risk" specialties for claim/year: Pathology, Dermatology, Family General Practice, Pediatrics, Psychiatry (mean 5%/year risk for claim). However, the authors also noted that the vast majority of malpractice claims did not lead to any indemnity payments.

Principal cause of a claim. According to Phillips and his colleagues [28], one-third of all claims was the result of misdiagnosis. In the US, in 1995, 24% of all patient claims and lawsuits were against Diagnostic Radiologists.

Outcome of liability claims against medical experts and costs. In US courts, more than 60% of liability claims are dropped, withdrawn or dismissed without compensation to the plaintiff (nevertheless, costing the defendant an average of US\$20,000). Medical Experts are found "not negligent" in over 90% of cases that go to trial (in 2008). However, the cost to defend these cases was more than US\$110,000 on average in 2008 [29, 30]. Cohen & Hughes [31] reviewed 18,452 cases between 06/1991-06/1992; of these, 69.4% were resolved in an agreed settlement, 23.7% had summary judgments, default judgments, dismissal or directed verdicts and 6.9% had trial verdicts. Among the trial verdicts, 26% were in favor of the plaintiffs. For the period 1995-2002, 41% of all claims

concerning “breast cancer and malpractice” received compensation of an amount of approximately US\$440,000 on average [32]. Additional litigation expenses (including lawyers, experts, and courts) and other transaction costs account for 55–60% of malpractice compensation expenses [33]. The US Department of Justice has found that median medical malpractice awards in the States range from US\$109,000 to US\$195,000 [31]. In general, direct and indirect costs of malpractice are between 5% and 10% of total US medical costs.

Medical Liability Premiums. They have increased by more than 1000% throughout U.S.A. (1976–2007) and more than double in 2008, compared to those of a few years ago [29, 30]. In New York and Florida, obstetricians, gynecologists and surgeons pay today over US\$100,000 per year for US\$1 million in coverage [33].

Finally, awards for medical malpractice claimants are subject to lengthy delays: on average, it takes around 4 years to resolve a malpractice claim [34].

TYPES OF LAWSUITS

The available literature on medical malpractice legal matters is rather restricted, originating mainly from the USA. Nevertheless, despite the fact that the legislation in different countries varies, the general guidelines related to malpractice remain the same. To prove malpractice and obtain the conviction of a defendant, the plaintiff should not only illustrate an unwanted result but must also show that the defendant HCP’s deviation from customary practice caused the plaintiff’s injury. The main types of lawsuits following malpractice are: Negligence, Gross Negligence and Deliberate or Intentional Torts. The same philosophy is also adopted for (medical) Product Liability [3, 11, 12, 19, 20, 21, 26, 28, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43].

Negligence

In any civilized country, people are legally entitled to receive a certain standard of medical care. In such cases, negligence generally arises when HCPs do not adhere to those standards. Negligence may be misfeasance, malfeasance, or nonfeasance.

Negligence is a type of tort based on “fault”. Fault in a tort context is not necessarily morally blameworthy: negligence is accidental as distinguished from “intentional torts” or from crimes; the conduct may not have been intended to cause harm but nonetheless failed to meet an accepted standard of conduct (often referred to as the “reasonable man” standard, see “Glossary of legal terms in medicine”).

Elements in determining liability for negligence

A person (a plaintiff) who alleges negligent medical malpractice must establish all elements of the tort of negligence in a malpractice lawsuit presented hereafter [43]:

1. A Duty of Care was owed (A legal duty exists whenever a hospital or health care provider undertakes care or treatment of a patient).
2. There is a Breach of that Duty (The provider violated the applicable Standard of Care or failed to conform).
3. The Breach of Duty was a proximate cause of an *Injury* (The person suffered a compensable Injury).
4. Damages were caused (The plaintiff suffered damage as a result of that Breach).

The legal burden of proving the elements of the tort (duty, breach of duty, causation of injury, and damages) is on the plaintiff.

1st element: Duty Defined by Standard of Care

The preexisting relationship between the defendant and the plaintiff must be such that there is an obligation upon the defendant to exercise reasonable care to avoid causing injury to the plaintiff in all circumstances of the case.

The basis of determining the standard of care has evolved from a “customary standard” (or “minimum standard of care”), based on practices of similar “reasonable and prudent” medical professionals, toward a more “objective” “good” standard (which should be the “minimally acceptable standard” [41].

Attention: “Accepted standards of conduct” change over time: Professional conduct on the part of a Clinical Oncologist, Radiation Oncologist or a Clinical Physicist that may have been “excusable ignorance” 15 years ago, may be regarded as “negligent ignorance” today.

From this perspective, Specialized Physicians (Oncologists, Radiation Oncologists, Radiologists, Surgeons and Others) and Radiation Physicists are considered as persons of exceptional knowledge, and held at a higher and more demanding standard of care of increased responsibility. A modern standard of care for medical professionals should be based on what [40, 44]:

- is reported in the international scientific literature ...
- professional, academic and medical schools teach ...
- various professional organizations or boards recommend (guidelines) ...
- other professionals do in their practices ...
- the expert witnesses recommend and do in their own practice ...

Among the above resources, the more solid and reliable, both legally and scientifically, and by far the best sources of guidance for the courts are guidelines and documents of the international professional bodies, as well as recognized authorities relative to the subject.

If there is not preexisting relationship between a Physician and a person, the former usually does not have a duty to render aid or prevent harm to the latter from an independent cause. Nevertheless, in some special circumstances, a Physician could voluntarily assume a duty like, e.g., on a road accident. Rendering aid to victims, the Physician is under a duty to exercise reasonable care and he or she is exposed to the risk to be sued for negligence.

2nd element: Breach of Duty

Dereliction or breach of duty generally refers to a failure to conform to rules of one's profession, which will vary by tasks involved. Breaching duty in medicine means that a doctor failed to react or act accordingly to a patient's illness or injury, or that an act he or she took was indeed negligent, and the outcome resulted in additional harm to the patient. Some of the types of legal claims regarding medical negligence and breach of duty are: prescribing incorrect medicines, administering incorrect drugs, incorrect Chemotherapy or Radiotherapy dosing, misdiagnosis, mistakes during surgery. As long as one of the accepted treatment approaches is followed, a doctor is protected from malpractice liability. Furthermore, the relative merits of each approach are irrelevant, provided that there is an established custom supporting the method employed [7, 12].

3rd element: Injury and Causation

Causation denotes a direct link between the defendant's negligence and the claimant's losses and damages. An added factor in the formula for determining negligence by the court is whether the plaintiff's losses and damages were "reasonably foreseeable" at the time of the alleged carelessness. In most cases, the defendant in a personal injury case tries to prove the opposite: that the plaintiff has a preexisting injury or that his/her injuries have some other cause. For example, assume that an Oncologist is sued for the negligent prescription (without being cautious for risks of severe high blood pressure) of bevacizumab (humanized monoclonal antibody that inhibits vascular endothelial growth factor A - VEGF-A) to a patient with metastatic colon cancer disease and that the patient died of a stroke. The plaintiff cannot recover damages for the stroke, unless there is sufficient proof to show that the wrong medication was a contributing cause.

Intervening Cause: In some cases, defense may argue that there was a prior intervening cause. A cause of injury is a superseding intervening cause only if it occurs subsequent to the defendant's negligent conduct. Suppose a defendant negligently treats a patient presenting a Ewing's sarcoma in the femur and subsequently, an orthopedist negligently treats also the plaintiff, aggravating his/her injury. The orthopedist's negligence is an "intervening cause" of the plaintiff's injury. It should be stressed that:

- Even if an intervening cause exists, it does not mean that the defendant's negligent conduct is not the proximate

cause of the plaintiff's injury. However, in some situations (defined and discussed in the court) the defendant will still be excused from liability.

- The defendant remains liable as he/she should have foreseen the intervening cause and should have handled it carefully and properly. However, if the intervening cause is the intentional or criminal conduct of a third person, the defendant is not liable for this person's negligent conduct.

4th element: Damage

Proof of damage is an essential part of the plaintiff's case. **Without damage (losses which may be pecuniary or emotional), there is no basis for a claim, regardless of whether the medical provider was negligent.** Likewise, damage can occur without negligence, for example, when someone dies from a fatal disease [20].

The plaintiff's damages may include compensatory and punitive damages (the last awarded only in the event of willful and wanton conduct). Below are presented elements of damages, which should be elicited when applicable in an injury or death case, arising from medical malpractice in general (a) and malpractice due to exposure to ionizing radiation (b):

a. Medical Malpractice elements of damages

- *Damages recoverable by or on behalf of an injured person:* medicines and medical fees, loss of past and future earnings, special care aid and equipment, travel expenses, assistance for household chores, care and assistance, adapted accommodation and transport, general expenses, pain and suffering from physical injuries and reasonably likely to occur in the future, mental anguish, harm or loss of sleep, sexual dysfunction, anosmia, past and future impairment of ability to enjoy life, ...
- *Damages recoverable by heirs or dependents of an injured person:* loss of consortium, loss of household services from killed or injured spouse, loss of financial support from decedent's earnings and other income, loss of parental advice and guidance, funeral and burial expenses, mental distress resulting from witnessing injury to decedent, ...
- *Additional elements of damages:* litigation fees and costs, damages for injury to real property, exemplary or punitive damages for malicious or irresponsible conduct...

b. Additional elements of damages due to Exposure to Ionizing Radiation

- *Exposure to radiation source:* nature of radiation source, level of exposure, proximity to radiation source, duration of exposure, exposure exceeded applicable regulatory standards, shielding (if any) of radiation source, protective clothing worn by the plaintiff at the time of exposure, license validity of the radiation unit at the time

of the event, valid calibration of radiation monitoring devices, ...

- *Standard of care*: breach of National and International Regulatory Standards, Standards created by oversight organizations, scientific research or industry.
- *Injuries*: acute radiation injury (erythema, wounds or open sores, damage to internal organs, death within accepted period following exposure), late radiation injury (cancer or leukemia, mutagenic and teratogenic effects).

Finally,

The court decides whether all elements of negligence [duty/standard of care, breach of duty, cause-in-fact / proximate cause (scope of liability) and damages] have been proven by a preponderance of the evidence (that is, by more than 50% to be more likely than not for anyone) to establish a prima facie case. If the plaintiff fails to prove one element of negligence, the plaintiff's case fails.

Gross negligence

Like many legal terms, gross negligence is difficult to define and has no generally accepted meaning. In general, it is a conscious and voluntary disregard of the need to use reasonable care, which is likely to cause foreseeable grave injury or harm to persons, property, or both [35]. Prosser and Keeton [41], state that:

"Gross negligence is more than ordinary inadvertence or inattention, but less perhaps than conscious indifference to the consequences".

Ordinary negligence and gross negligence differ in the degree of inattention, while both differ from willful and wanton conduct. In addition, a finding of willful and wanton misconduct usually supports a recovery of Punitive Damages, whereas gross negligence does not. Examples include a surgeon amputating the wrong limb or leaving a surgical instrument inside a body cavity of the patient.

Physicians and Physicists should be very concerned when gross negligence is pleaded in any lawsuit, because malpractice insurance may not cover awards of exemplary damages.

"Gross negligence" in the Civil and Criminal Law requires from a plaintiff at least a "clear and convincing" standard of proof, which is a standard greater than the "preponderance of evidence" standard.

Deliberate (intentional) torts

Although most medical suits involve negligent torts, there is significant opportunity for suits charging deliberate (intentional) torts. To establish the required intent to support such a charge, it is not necessary to show that the defendant specifically meant to harm the plaintiff but only that the defendant deliberately performed the wrongful act. For example, a Physician can be accused [12] of intentional tort

in the case of abandonment, disclosure of confidential information and fraud.

The following are the most significant types of deliberate torts in the medical arena:

Battery: It is defined as the intentional violation of a patient's rights to direct his or her medical treatment. The wrongful act to be avoided under battery is the invasion of a person's right of bodily inviolability. Medical battery occurs when a patient is treated without informed consent. Most commonly, battery charges are alleged where there is a dispute over whether the patient agreed to treatment or refused it. The agreement or refusal of treatment can be made directly with the patient, through an advance directive, or through a health care proxy. A valid ground for complaint exists even if the defendant intended no harm and the patient suffered no physical damage. Monetary awards generally are small unless there is physical damage or the defendant meant to cause harm. Cases of alleged sexual assault by Physicians are considered battery actions.

Fraud and deceit: Cases in which a Physician deliberately misrepresents facts to obtain a patient's consent for a procedure are treated as matters of fraud and deceit. These cases can be distinguished from the more common cases of informed consent. To show that a doctor committed fraud or deceit, whether in giving advice to the patient or altering clinical records, the plaintiff has to show the following:

1. The doctor knew, or should reasonably have known, that the information was false or that the records were altered.
2. The doctor intended that the patient relies on it, and he or she believed it was true.
3. The patient based his/her decision or action on the belief that it was true.
4. The patient suffered an injury or financial loss because of his/her reliance on the doctor's misrepresentation. For example, the patient consented to surgery or delayed filing a malpractice suit until after the time limit ran out.

Breach of confidentiality: Disclosure of information about a patient's case to a third party, without patient consent or court order, of private information that the Physician has learned within the patient-physician relationship. Disclosure can be oral or written, by telephone or fax, or electronically, for example, via e-mail or health information networks. The medium is irrelevant, although special security requirements may apply to the electronic transfer of information. This theory can support a suit based on an implied duty to keep patient information confidential, invasion of privacy, defamation, and unprofessional conduct.

Fee splitting in medicine & healthcare

In the case of fee splitting the law states "that payment by or to a Physician solely for the referral of a patient is unethical as is the acceptance by a Physician of payment of any kind,

and in any form, from any source such as a pharmaceutical company or pharmacist or a manufacturer of medical appliances and devices, for referring a patient to that source. ... Clinics, laboratories, hospitals or other health care facilities which compensate Physicians for referral of patients are engaged in fee-splitting, which is unethical" [AMA code, 30].

In most parts of the world, this practice is also considered unethical and unacceptable, and one of the major reasons of medical malpractice [7] as:

- patients will not necessarily be referred to the most appropriate doctor to provide care, but will instead be referred to those doctors or hospitals with which the referring doctor has a commission payment type of arrangement;
- it encourages a care provider to provide unnecessary treatment, prescribe expensive unnecessary expensive drugs, and run tests.

PRODUCT LIABILITY

Product Liability or Medical Malpractice? *Many times, drug providers and medical device manufacturers fail to warn about the potential dangers of their products and fulfill their duty by providing the warnings to the medical personnel who will be using the products, and then the duty passes to those professionals to inform the patient. There is a fine line between a products liability action involving a defective medical device and a medical malpractice action [www.injury.findlaw.com].*

Negligence (duty and breach of duty) may not be easily proven against a distant manufacturer of a product that has caused harm. In the majority of these cases no liability has been found, as manufacturers claim that their "activity and responsibility" was ceased at the time of the initial distribution of the product to intermediaries. Product liability, based on strict liability, is a more accessible target for a plaintiff injured by a product (focusing upon the product rather than the intent to actions to provider/ manufacturer/ seller) [3, 12].

The four principal arguments that underlie product liability suits are a) Negligence, b) Breach of Warranties, c) Strict Products Liability, d) Misrepresentation or Defectively Marketed Medical Devices.

The Plaintiff (Hospital, HCP, Patient) must prove that the product (medical device/ drug):

- a. Was legally sold (the plaintiff must identify the supplier of the defective product and establish a causal relationship between product and plaintiff's injury).
- b. Reached the user without change. This can be assured only if the product is delivered accompanied with signed proof at the final place of use (e.g. hospital) and not at the manufacturer's store or factory (otherwise,

the seller may allege that the damage occurred during the transfer from the seller's site to the user's place).

- c. Was defective in design, manufacturing, or lack of warning (rendering the product malfunctioning or unreasonably dangerous as perceived by a user) and the defect has existed at the time the product left defendant's control.

In addition, the Plaintiff must show that,

- d. There were proximate injuries and damages caused by the defect.
- e. More probably than not, the defect did not arise from subsequent improper handling or misuse of the product.

Nevertheless, the overall scheme is ambiguous: a plaintiff may recover damages even if the seller has exercised all possible care in the preparation and sale of the product, but even under strict tort liability principles, a manufacturer/ seller is not an insurer of the safety of the products he/she sells.

Prescription of drugs and medical devices

These medical products are not defective in design as long as they would be sufficiently therapeutic to prompt a reasonable health provider, knowing its foreseeable risks and benefits, to prescribe the drug or the radiotherapeutic session. Some drugs, in the present state of human knowledge, are not completely safe for their use. The designation of a drug or a medical device as "unavoidably unsafe" does not protect completely the health provider, as the plaintiff may still prove liability in negligence upon showing that the product, usually a pharmaceutical, was marketed without due care. Nevertheless, in many instances it is sufficient to materialize the chain: the manufacturer warns the prescribing health professional about the potential risks, the latter is conscious that he/she is not in a position to reduce the risk and reasonable warnings are directed toward the patient.

A post-sale duty to warn arises "when a latent defect which makes the product hazardous becomes known to the manufacturer shortly after the product has been put on the market". The manufacturer has also a continuing duty to warn and to apprise of new scientific and medical developments, and to inform the medical profession of pertinent developments related to treatment and side effects.

Basis for liability

The manufacturer or/and seller of a medical device or drug is presumed to be an expert in his/her field. The duty to guard against negligence and supply a safe medical product applies to everyone in the distribution chain, including the manufacturer and the vendor. These individuals owe a duty of care to anyone who is likely to be injured by such a product

if it is defective, including the initial buyer (hospital or HCP) and the end-user (patient) [45]. In sum:

- Warnings: Sellers have a duty to warn for hazards of which they know or have reason to know, and of which the buyers are unaware.
- The occurrence of an unwanted event itself does not make out plaintiff's *prima facie* case in negligence. However, circumstantial proof, such as recent purchase and ordinary use, that tends to rule out the possibility of alternative causes, may advance the plaintiff's proof of both defects and negligence.
- Defendant's violation of a regulation pertaining to safety may be considered negligence *per se*.
- Upon the demonstration that the product was one over which the defendant had complete control (e.g. linear accelerator under contract of maintenance), and that the accident resulting in injury was of such a nature that it ordinarily would not occur in the absence of negligence, the doctrine of *res ipsa loquitur* permits the plaintiff to shift to the defendant the burden of proof on the issue of negligence.

At common law, a defendant (usually a manufacturer or seller) could defend in negligence by showing that:

- Liability in negligence is limited to settings, in which the product was put to a reasonably foreseeable use, including a reasonably foreseeable misuse.
- Implied warranties of merchantability or fitness for a particular purpose can be disclaimed, provided that the seller carefully follows the disclosure and protocols established.
- Subsequent product changes, or other post-incident remedial measures, cannot be used by plaintiff to prove defect or antecedent negligence.
- No duty exists to warn for obviously hazardous conditions.

LITIGATION IN ONCOLOGY

Potential areas of litigation

Oncologists are less likely to be sued than Physicians of other specialties. As the nature of the specialty relates to plenty of bad outcomes, Oncologists are perhaps protected from allegations of wrongdoing by the fact that most such allegations are not unexpected. Therefore, they must be aware of medico-legal vulnerability and avoid exposure to allegations of negligence. The potential areas of litigation described below, in large part concern not only Oncologists but also other cancer specialists and Health Care Professionals [39].

Cancer diagnosis mistakes

There are several ways in which Oncologists can make diagnostic mistakes. The most important ones are: missed diagnosis, wrong diagnosis (misdiagnosis), failure to recognize complications, failure to diagnose a related or

unrelated disease and delayed diagnosis. Late diagnosis (breast cancer being the leading cause) and misdiagnosis are the more common types of diagnostic errors and hold a large percentage in medical malpractice complaints. The usual causes of delay in cancer diagnosis involve [36, 37, 39]:

- Weak communication and cooperation between the Diagnostic Physician (Pathologist or Radiologist) and the ordering Physician [46], or between Physician and patient.
- Misreading of pathology slides.
- Failure to follow a symptom or biopsy a mass after initially negative tests.
- Missing second malignancies in cancer survivors, who are at increased risk due to both genetic predisposition and to late side-effects of treatment.

Chemotherapy prescription and dosing

It concerns errors in Chemotherapy prescribing, mixing, and administration. A positive aspect on this matter is that oncology chemotherapy drugs have a lower therapeutic index than drugs used in other specialties. A negative aspect is the tremendous regimen complexity involving several calculations, consideration of organ function and patient age, previous drug exposure, toxicities, specific patient characteristics, numerous critical supportive drugs and procedures, and drugs to protect against toxicities of specific agents.

In addition to the above, recent changes in chemotherapy services, drug provision, preparation and administration not directly controlled by the Oncologist (e.g. movement of chemotherapy administration out of the oncology offices), phone calls, insurance issues, regulatory demands, and declining reimbursement increase the risk of error and, hence, liability [39, 47].

Experimental treatments

The well-known High-Dose Chemotherapy plus Autologous Bone Marrow Transplant (HDC-ABMT) breast cancer treatment procedure [48] controversy bears two important lessons for resolving disagreements about experimental treatments:

1. It underscores the importance of fidelity to good science as the primary basis for using and paying for a new medical intervention. Medical and financial coverage for a, very often, costly and toxic treatment when its efficacy is unproven, has serious ramifications for patients, clinical researchers, and the health care budget.
2. The controversy raises questions about the institutional competence of courts to resolve coverage disputes concerning investigational therapies.

Based on the principles of beneficence and non-maleficence, if the efficacy of a treatment is not substantially proven and involves high morbidity and mortality, the Physician should avoid recommending it. However, treatment decision approaches by patients and their Physicians may differ. Indeed, the

relevant question to scientists and insurers is whether there was reliable evidence that a new drug has therapeutic benefit. To desperate cancer patients who have not responded to conventional treatment options, it is a last chance intervention and the question is whether the procedure might have benefit.

This controversy shows that there are major limitations on the usefulness of litigation as a means of resolving disagreements about investigational treatments. If health plans resist pressures to provide coverage for expensive new therapies that are not yet proven by well-designed clinical trials, inevitably more patients will turn to the courts for relief. Thus, the safest way to avoid litigation is good science and participation in clinical trials, determining the medical appropriateness of experimental treatments.

Radiation dose

Current radiation safety philosophy is based on the conservative assumption that radiation dose and its biological effects on living tissues are modeled by a relationship known as the "Linear Hypothesis". The assertion is that every radiation dose of any magnitude can produce some level of detrimental effects, which may be manifested as an increased risk of genetic mutations and cancer.

This assumption led to the acceptance of the concept "ALARA", acronym for "As Low As Reasonably Achievable". "Reasonably" including economic, social and technological factors. This is a radiation safety principle for minimizing radiation doses both to patients and to radiation personnel and releases of radioactive materials by employing all reasonable methods. However, ALARA is not a tort standard of care; rather, it is a professional philosophy of excellence.

Duty of Care & Breach of that Duty: Many radiation injury cases that find their way to court are based on the tort theory of negligence. The duty is easily proved in these cases and is difficult for a defendant (Radiation Specialist) to successfully agree a "no duty" defense, as the use of radiation is highly regulated. Regulations play a major role in defining the standards of care in Radiation Protection (dose limits) and in Radiology (performance-based imaging quality) [46]. In Radiation Therapy, regulations have lesser importance in defining the standard of care, because of the individualized nature of the treatment (technique, treatment site, radiation dose and dose rate). Compliance/ Non-compliance with safety standards in this well-structured and highly regulated area provide an excellent measure of breach.

Causation & Injuries: An HCP (as defendant) who has attentively complied with international and national radiation regulations might successfully argue that an injury that resulted, despite the compliance with the above standards and regulations, was no "foreseeable" and was, therefore, beyond the defendant's duty. The defendant should not have a duty to protect against unforeseeable immediate or late injury. Regarding late radiation injuries, the situation is more complicated. Although medicine recognizes a causal link between

radiation and late effects, this does not mean that everyone exposed to radiation will develop cancer or leukemia. Moreover, no medical tests exist that can determine that late injuries were caused specifically by radiation [12, 44].

It is extremely important to emphasize that:

- a "poor" therapeutic result, standing alone, is not proof of negligence (for instance, when a Radiation Oncologist handled his/her patient with reasonable care, diligence, and judgment);
- measurement or calculation mistakes are not considered as "errors in judgment" per se. Mistakes in radiation measurement or calculation that result in injury and damage to a patient will be found to be "negligence" on the argument that a safety system should have been in place to discover errors.

Pain control

The successful practice of hospice and palliative medicine requires basic knowledge of its medico-legal aspects [49]. Oncologists face liability for over-/under-prescribing narcotic analgesics, especially if this results in patient death. However, as guidelines for pain management are available, e.g. American Pain Society [50], Physicians are usually protected against negligence if they comply with them.

Informed consent

Patients often have expectations of medical outcomes that do not coincide with actual success rates. Oncologists who give false hopes or promise a cure further add to this problem. Adequate informed consent and honest communication are always essential. No matter what standard is applicable and before the patient can give consent, there are five basic elements that must be disclosed in language that a lay individual reasonably can be expected to understand [15]:

1. The diagnosis, including the disclosure of any reservations the Oncologist could have.
2. The nature and purpose of the proposed procedure or treatment.
3. The risks and consequences of the proposed procedure or treatment.
4. Reasonable treatment alternatives.
5. Prognosis without treatment.

Often a number of informed consent cases are based on negligence, when an Oncologist performs a substantially different procedure from that to which the plaintiff-patient agreed or, when the doctor significantly exceeds the scope of the plaintiff-patient's consent [10]. Nevertheless, the typical negligence-based informed consent case occurs where an undisclosed complication with a medical procedure or treatment arises. The Oncologist risks being accused for loss of chance of a better result for the patient, if a more expe-

rienced Oncologist had performed the procedure or a different therapy had been chosen.

An Oncologist would not be liable when the non-disclosure of a material risk was justified due to an emergency (a victim is unconscious and unable to provide consent) or when the patient requests the doctor not to inform him or her. Many courts also recognize a therapeutic privilege under which an Oncologist may justify non-disclosure upon proof that disclosure of information would be harmful to the patient's physical or psychological well-being.

Based on the above elements, to succeed in a claim of negligence the patient must show that:

- the Oncologist failed to inform the patient adequately of significant risks of serious harm associated with the proposed treatment, as well as alternatives;
- the patient, due to this failure, agreed to therapy that a reasonable patient would otherwise have refused;
- the patient suffered injury due to the therapy subsequently received.

Since medical treatment requires consent, the determination of the effective actual consent is critical in this context. A medical procedure without the patient's consent can constitute battery. These elements may seem obvious, however the criteria are less well-defined for Chemotherapy or Radiation Therapy, especially as practices vary among countries and in many of them a formal written consent form is not required.

Generally, legal protection and good medical practice require:

- A detailed explanation of risks and benefits before beginning treatment,
- The documentation of that explanation should be added the medical record. This includes "diagnosis, nature, consequences and alternatives of the proposed treatment, prognosis with and without the treatment". Without this record, even a note "informed consent obtained" or better a signed consent, are not sufficient to protect the Physician against suit.

The way to speak to patients about their diagnosis, treatment and prognosis clearly without frightening them and avoiding emotional trauma is a major challenge. These matters become even more complex when dealing with:

- mentally impaired or incompetent patients;
- children and parents, in pediatric oncology;
- desperate patients in oncology research. These patients may confuse research and treatment and have unrealistic expectations about benefits. ASCO offers guidance in its policy statement on oversight of clinical research [51].

Protection of privacy

It is very important for cancer patients to maintain confidentiality of medical information and records, avoiding informing the family and/or others until patient consent can

be obtained. Improper disclosure of this data could result in emotional, psychological, and financial harm to patients and their families. Specific regulations and laws determine to whom cancer information may be reported, how cancer information is reported, and what procedures should be taken to access cancer information. Particularly risky is also communicating HIV or genetic testing results and familial diseases [2, 39, 52].

For patients of an Institution (usually hospital), care and treatment are recorded. This information is shared with the health care providers involved in the case and part of it with the Financial and the Statistics Departments of the Hospital. "Health Care Providers" in this context are Departments and Units of the Hospital, including Outpatient Clinics employees, volunteers, trainees, students, contractors and medical staff members of the Hospital, involved in the treatment. The data is not used or disclosed for other purposes without the patient's permission.

Exception to the above rule: Under specific circumstances (some with and some without the patient's permission), medical information can be disclosed to Appointment Reminders, Treatment Alternatives, Health-Related Services, Hospital Patient Directory, Spiritual Care Services Office, Individuals (family members or friends) involved in patient medical care, Coroners, Medical Examiners, Funeral Directors, Organ and Tissue Donation Organizations, Military Command Authorities (for members and veterans of the armed forces), authorized National Officials for Intelligence, Counterintelligence, and other national security activities authorized by law, Correctional Institutions or Law Enforcement Officials (for inmates or persons involved in a lawsuit or a dispute), Research Coordinators, Public Health Authorities (for the protection of the public health), Police Authorities (to prevent a Serious Threat to Health or Safety).

Regarding medical records, the patient has the right to [2]:

- Inspect and Obtain a Copy (subject to certain limited exceptions, e.g. it may not include some mental health information).
- Request a Correction or add an Addendum (if the patient believes that the file is incorrect or incomplete).
- Request an Accounting of Hospital Disclosures of the Medical Information (list describing how the hospital has shared medical information with outside parties).
- Request Confidential Communications (about medical matters in a certain way or at a certain location).
- Request Restrictions (on certain uses or disclosures of the medical information, e.g., the patient's name not appearing in the Hospital's Patient Directory while inpatient).

Genetic counseling

With the growing availability of tests for genetic predisposition to malignancy, patients are increasingly turning to their oncologists for advice on whether to test and what to do with test results. One could be held liable for omitting indicated

testing or neglecting to maintain surveillance for an associated cancer. There is equal need for full disclosure if a patient rejects a procedure recommended by the Oncologist. In this case, a practical and useful step is to write a letter to the referring Physician and send a copy to the patient.

Oncology Societies [53, 54] affirm their will to integrate cancer risk assessment and management, including molecular analysis of cancer predisposition genes, into the practice of oncology and preventive medicine (especially for patients and families affected by hereditary cancer syndromes). It is recommended that Oncologists should include in pre- and post-test counseling the discussion of possible risks and benefits of cancer early-detection and prevention modalities, some of which have presumed but unproven efficacy for individuals at increased hereditary risk of cancer.

Defense to liability

Almost all malpractice cases involve a serious injury, complication, or death. Juror sympathy for the plaintiff is highly probable. The first duty of the defense is to try to accurately assess the case at the earliest possible stage with the assumption that the case will go to trial. The initial inquiry from the plaintiff side is whether there are any immediate defenses to be raised by the defendant's side (i.e., improper venue, statute of limitations violations, etc.). Then, both sides turn to the charges themselves [62]. The most important of the above parameters are presented in brief below.

Contributory negligence, comparative negligence and assumption of risk

Even if a plaintiff has established that the defendant owed a duty to the plaintiff, breached that duty, and proximately caused the defendant's injury, the defendant can still raise defenses that reduce or eliminate his/her liability. These defenses include [14, 38, 45, 63]:

- **Contributory Negligence:** It applies to cases where plaintiffs/claimants have, through their own negligence or incautious conduct, contributed to the harm they suffered.
- **Comparative Negligence:** Partial legal defense that reduces the amount of damages that a plaintiff can recover in a negligence-based claim based upon the degree to which the plaintiff's own negligence contributed to cause the injury.
- **Assumption of Risk:** Avoid liability for negligence by establishing that the plaintiff voluntarily consented to encounter a known danger created by the defendant's negligence.

Circumstantial evidence

Sometimes a patient (plaintiff) has no direct evidence as to how the defendant (doctor) acted and must attempt to prove his/her case through circumstantial evidence. Suppose that a patient with breast cancer is severely injured during a surgical operation to remove the malignant mass of tissues.

The plaintiff, who was unconscious during the operation, sues the doctor in charge of the operation for negligence, even though she has no idea how the injury actually occurred. In cases such as this, the doctrine of "*Res ipsa loquitur*" ("the thing speaks for itself") is invoked. "*Res ipsa loquitur*" allows a plaintiff to prove negligence on the theory that his/her injury could not have occurred in the absence of the defendant's negligence [14, 63, 64].

One should keep in mind: the Jury will be constantly looking at the defendant throughout the trial, assessing his/her every move even when he/she is not on the witness stand [62].

Defendant doctor's deposition

As the line between conduct which meets the "standard of care" and conduct which is outside the standard of care, is often thin, blurred (and potentially still evolving), the defendant doctor's deposition is the most important part of preparing the defense case. This is a challenge and a risk for the defendant's lawyer as, despite extensive pre-deposition preparation, even the most intelligent and savvy Physicians still remain unpredictable once the deposition begins, and may yield to the temptation of saying too much [62]. The Less Said the Better: the testimony should be kept as short as possible, scoring important points and being interesting [65, 66].

"The role of expert witness is alien to most Oncologists, who are accustomed to quoting evidence from studies, but who may instead be asked to comment on questions for which data are incomplete or nonexistent. For example, cases alleging delay in diagnosis often hinge upon retrospective estimates of survival based on different times of diagnosis and treatment. Scientific concepts like lead-time bias, relative versus absolute risk, and statistical versus clinical significance may be difficult to convey to a lay audience. Attorneys may try to elicit absolute percentages of survival or tumor doubling times, rather than the sort of speculative, qualified estimates with which Oncologists are more comfortable" [39].

Alternate Dispute Resolution: 60% of available funds is expended on administrative costs (mostly legal fees), rather than patient compensation [69]. To address these problems, a number of alternative processes have been proposed [39]:

- Giving an apology to the patient and reassurance that steps will be taken to prevent recurrence is often effective in averting a claim of malpractice. Nevertheless, such an apology may legally constitute an admission of guilt.
- Improve quality of evidence and consistency of decision-making by involving experts [44] in the adjudication.
- Settlement between litigants shortly after an adverse event.
- Proceed through arbitration instead of resolving disputes in court. Arbitration involves the selection of one or several neutral persons by the litigants. These arbitrators then hear the case and render a decision about any award.
- Predetermined compensation for avoidable bad outcomes

(this proposal is strongly rejected by the trial bar for financial reasons...)

- Other methods summarized well elsewhere [42].

AVOID LITIGATION

Medical Doctors and Health Care Professionals ARE NOT lawyers, do not wish to be lawyers, have no free time to learn jurisprudence and feel illiterate, when facing this scrabble of juristic sentences and legal and semantic traps. Avoid or confront litigation, principally via legal means, is the "abrupt and very uncertain way to heaven" for health scientists. The easy way is presented below. However, in this case as well, dilemmas still exist and do trouble medical doctors.

Defensive medicine (not recommended...)

Theoretically, the medical malpractice liability system has two basic objectives: a) to compensate patients who are injured through the negligence of health care providers and b) to deter providers from practicing negligently. By most standards, the system does not achieve these objectives, as it drives many students away from entering the medical field, Physicians out of business and oblige many doctors to practice "defensive medicine" ("Positive" or "Negative") in order to avoid malpractice suits [10, 9].

Positive defensive medical practice is the over-reaction to the malpractice threat and theoretically has a favorable impact on the quality of care received by the individual patient. On the other hand, precautions and treatment based on fear of legal liability rather than the patients' best interest, are often inappropriate and costly. Such practices are increased screening, development of audit or consumer satisfaction activities, and more detailed patient explanations or detailed note-taking.

Negative defensive medical practice presents serious quality as well as quantity implications, as it consists of Physician refusal to undertake activities, which have a high risk of resulting in malpractice litigation. This leads hospitals and HCPs to neglect taking appropriate precautions to avoid harming patients. Such practices are prescription of unnecessary drugs; increase in follow-up, referral rate and diagnostic testing; avoidance of patients with complicated problems, high-risk procedures, new and innovative medical procedures; or implementing more efficient organizational techniques, such as employing Physician's assistants or delegating functions.

The end result of the so-called "defensive" medicine, driven by liability fear, is a potentially serious social problem: restriction of patient access to health care and the offered treatments are probably not beneficial, inefficient and finally dangerous to the patient.

Liability pressure on defensive medicine increases health system costs by hundreds of billion euros per year worldwide. According to the various studies and especially the Harvard Medical Practice Study [10, 21, 29] in the USA:

- Only 1 in 15 patients who suffer an injury because of medical negligence receive compensation, and 5 in 6 of the cases that receive compensation have no evidence of negligence.
- Defensive medicine increases health systems costs by US\$84 to 151 billion each year.
- 1 in 12 of obstetricians who have reported changes in their practice due to the risk of professional liability claims) has stopped delivering babies.
- About 1 in 2 Physicians in Massachusetts has altered/limited his/her services because of the liability fear.
- Numerous scientific publications show that patients have greater access to Physicians in areas with reforms (e.g., limits on non-economic damages), than in areas without.

Policy changes that could enable doctors, hospitals, and patients to voluntarily opt out of the tort system, reduce the prevalence and cost of defensive medicine [10, 39]. In particular, reforms such as caps on damages reduce malpractice pressure, and in turn, defensive medicine. For example, by reducing claims rates and compensation conditional on a claim, medical expenditures could be reduced without any increase adverse health outcomes.

"Healthy" medicine (recommended)

"State of the art" consultation, preparation, planning and execution of a treatment require a combination of quality assurance mentality, good patient-physician communication, careful records' keeping and tracking system for follow-up, cooperative teamwork, revealing own errors, avoidance of defamation, and others, which are presented briefly hereafter.

Quality assurance

The major aim of developing Quality Assurance Mentality and Procedures, and Quality Control Tools should be to improve the quality of care delivered by health care providers rather than to avoid litigation (even if avoid litigation is synonym to good practice). This mentality is materialised by:

- applying the best available, clear, reliable, effective, clinically applicable, valid and under standardized criteria practice;
- revising the practice when new scientific evidence emerges or if consensus changes;
- maximizing training, research and education profits;
- decreasing practice variation, harm to patients, and professional misconduct;
- not adhering to ineffective practices and outdated recommendations and not using low quality scientific technics.

Oncology involves a very complex process each stage of which may be prone to mistakes, deviations or variation in results interpretation. Each of these processes must comply with internationally accepted quality criteria [5, 6, 8, 25, 70, 71].

Physician and patient relationship

If there is no trust in the doctor-patient relationship, the patient will be more likely to question both the competence and recommendations of the doctor when an adverse outcome does occur. Trust must be earned, and it begins with the establishment of a good patient-physician relationship. Patients rarely bring tort action against providers they trust and like or perceive as trying their best to serve them [15]. Trust involves good communication. Poor communication results in many misunderstandings and misguided expectations. Moreover, one of the reasons why patients sue their Physicians is the patients' perception that their viewpoint was ignored. The Physician should [72]:

- Listen to patient's questions, answer and take into account his/her preferences regarding treatment (e.g., aggressive treatment for small gains in survival, or the reverse).
- Apply effective communication, e.g. patient satisfaction leaving consultation, high use of open-ended questions, great empathy, use of psychosocial probing.

The office staff is part of the communication system too, and must be well-trained in courtesy, safe triage, and privacy safeguards.

Medical records

Records deficiencies and/or amendments are interpreted by the courts as fraudulent. Many negligence cases are lost due to [39]:

- Incomplete, illegible, or missing medical records.
- Altered or destroyed records by HCPs or hospital employees.
- Late corrections of a record. This assumption concerns especially groups of doctors, who attempt to correct each other's records without meticulous annotation of when and why.

Electronic medical records may help but maintenance of confidentiality is one obvious challenge [19]. Good medical record keeping also extends to phone calls and laboratory and x-ray reports. Patient care records are the property of the employer (e.g. hospital), who has a legal duty to maintain the records intact. Removal of these records by a medical expert leaving the hospital, can place the institution in a very difficult position both clinically and legally with regard to previously treated patients [12].

Tracking systems for follow-up

The accurate and timely flow of information between patients and health care providers is important for safe and effective care. Patient visits to Physicians often require some form of follow-up that involves further screening, referrals, communication of test results, or consultations. Oncologists have the additional duty to ask for a wide array of data for their patients' actual treatment or/and follow-up, including e.g., blood counts, regular ECGs, coagulation parameters, liver and kidney function, scans, tumor markers, mammo-

gram, etc. Failure to follow-up may cause delayed or missed diagnoses or treatment.

Courts have held that the health care professional is responsible for contacting patients about laboratory, imaging, and consultation results; however, patients have the responsibility to follow through on their health care providers' recommendations. Nevertheless, they may find themselves held liable if patients fail to follow through, and then are not contacted by the office. Similarly, if patients fail to keep appointments, and there is no record of efforts to contact them to reschedule, they may prevail in a claim for negligence if they later develop some problem. Failure to follow up on laboratory results has been identified as one of the leading causes of lawsuits in the outpatient setting.

Oncologists and other HCP offices should have procedures in place to track these events effectively and enhance the quality of care and patient safety. An adequate tracking and reminder system can help reduce risks and provide safe, high-quality patient care [73].

Cooperative teamwork

"Collaboration involves coordination of individual actions, cooperation in planning and working together, and sharing of goals, planning, problem-solving, decision-making, and responsibility" [74]. Unfortunately, health care providers tend, in general, to strongly identify with their own discipline and its language, values, and practices and to best relate to members of their own discipline [75]. Cross-disciplinary communication can be complex for this reason, but increased specialization contributes to the need for collaboration between experts in different areas of knowledge and furthermore, it is professionally needful and beneficial to patients [76].

In order to reduce treatment errors (especially in Chemotherapy and Radiation), the essential requirement is communication accuracy among all parties caring for cancer patients [12, 39, 77]. Oncologists should avoid verbal orders and personally inspect their own prescriptions and orders, as well as encourage the expression of any logically or/and scientifically based disagreement among their coworkers, in the interest of preventing errors. Specifically regarding the safe prescription of oral Chemotherapy drugs, Birner *et al.* [47] go so far as to recommend that Oncologists "write non-refillable prescriptions only for the amount of medication necessary to complete one cycle of Chemotherapy". Suggestions include also multiple levels of order recalculation and verification; dose limits, order simplification and standardization; computerized physician order entry, dedicated oncology units, patient and family education [39].

Need to reveal own errors in a teamwork

This issue is important, especially for systematic errors like those that could be made e.g., by Radiation Physicists in Radiotherapy. Many Radiation Physicists have discovered their own mistakes (which may relate to a patient or may be

systematic that have affected previous patients) and some of them have concealed these mistakes. If the above HCP is unwilling to reveal past errors, the skill of the Radiation Oncologist may be undermined in treating new patients because of a faulty association of dose prescriptions and the expected clinical result (e.g. a systematic delivery of 50Gy – underdose of the lesion – instead of 70Gy for solid epithelial tumor cases, could guide a Radiation Oncologist to the erroneous conclusion that a dose of 70Gy is not adequate for the treatment of such cases). Taking into account the avoidable incertitude in Radiation Therapy (guidelines define as $\pm 5\%$ of the prescribed radiation dose) which is well known and consequently not necessarily communicable, the Radiation Physicist is under an ethical obligation to reveal any discovered error outside the above limits [12, 78].

Prevent harm to a patient

Any HCP has a responsibility to call attention to anything (including Physician orders) that may harm a patient. If a dispute cannot be resolved inside the department, the HCP should take the question to a higher authority. If there is no higher authority, the HCP or employee may provide some self-protection by submitting their concerns in writing to the chief Physician or his/her superior. However, it must be made clear to the staff that the treating Physician is the final responsible for medical decisions.

Avoidance of defamation

Oncologists often receive requests of advice about patients whom they have not actually been asked to see. One of the unethical but certain ways to drive, as plaintiff, a patient to court is to devaluate and discommend a colleague's medical treatment. Additionally, advising patients to seek a second opinion (especially in the middle of a treatment course) is not always sincere and may result in the loss of confidence to all Oncologists.

Disagreements on the actual treatment plan are likely to occur, however one should be very careful when criticizing the expertise or judgment of the previous Physician, and by no means should this criticism be expressed to the patient or registered in the medical record. Providing such consults, aside from considerations of ethics and courtesy, bears considerable risks, as the related patient data is usually incomplete. Furthermore, one should act thoroughly for self-interest purposes, because if a lawsuit takes place, the criticizing Physician would potentially be involved along with the prior Physician [39]. If the case is straightforward, one might go ahead and give advice, but ask to be anonymous, for medico-legal reasons. If the case is in the least complex,

however, one should ask to see the patient officially.

EPILOGUE

Justified or not, many patients or their relatives, turn to courts, accusing Oncologists and other Healthcare Providers for delayed diagnosis, overexposure to ionizing radiation, injuries, etc. Judicial prosecutions for malpractice are nowadays common practice in the USA and over the last years, this practice has gradually spread in Europe as well, causing disturbance and stress in the medical and oncology community. Many Physicians, including Oncologists, were forced to practice "defensive medicine" as a guard against malpractice claims.

On the other hand, this new status presents a number of advantages: it activates and prompts Healthcare Specialists to take care of patients more thoroughly, to respect medical procedures and clinical protocols, and overall to improve the quality of the healthcare services provided. This subject should be the starting point for questioning and further deliberation on how standards of care and quality assurance procedures may protect the related medical specialties from mistakes and malpractice. Fortunately, most of the methods for avoiding malpractice suits simply amount to providing good patient care.

Responsibility

- Taking responsibility is the mark of a professional, as opposed to a worker, who may do complex functions but often does not take responsibility for the final result.
- An HCP who accepts responsibility does not have an excuse for not fulfilling that responsibility.
- To avoid mistakes and psychological pressure leading to errors and malpractice, the number of staff and training needs should be reviewed whenever the workload increases, a new machine is purchased or a new technology or treatment technique is introduced. Overwork or lack of equipment are not legal excuses for failure to uphold a responsibility.
- An HCP should define the conditions under which he or she accepts responsibility. The earnings of a professional are more related to the responsibilities taken than to the hours worked and the technical complexity of that work.

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Conflict of interest statement

The author declares no conflict of interest.

GLOSSARY OF LEGAL TERMS IN MEDICINE

Assault and battery	<ul style="list-style-type: none"> ■ Assault: Act that creates an apprehension in another of an imminent, harmful, or offensive contact. The act consists of a threat of harm accompanied by an apparent, present ability to carry out the threat. ■ Battery: Harmful or offensive touching of another.
Board actions	Non-disciplinary actions imposed upon a doctor based on a complaint investigation. A patient or medical colleague may file a complaint with that state medical board or professional licensing organization, which then investigates the complaint. Board actions are intended to ensure that a doctor is able to perform safe medical and health care tasks.
Bodily injury	Recognizable injury to the organism.
Causation in fact	The defendant's negligent conduct is a cause in fact of the plaintiff's injury if, as a factual matter, it directly contributed to the plaintiff's injury and without it plaintiff's injury would not have occurred. It is not necessary that a defendant's act be the sole cause of plaintiff's injury, only that it be a cause.
Compensable injury	Injury caused by an accident arising from the employment and in the course of employee's work. Injuries can occur during medical treatment for the original compensable injury.
Dangerously defective medical device	Medical device which a Reasonable Health Care Professional (R-HCP) would not put into the stream of commerce if he/she had knowledge of its harmful character. "Unreasonably dangerous" is an article dangerous to an extent beyond that, which would be contemplated by the ordinary consumer who purchases it, with the ordinary knowledge common to the community as to its characteristics.
Defensive medicine	Defensive medicine occurs when doctors order tests, procedures, or visits, or avoid high-risk patients or procedures to reduce their exposure to malpractice liability.
Design defects	Medical devices that were properly manufactured but have an unreasonably dangerous defective design which results in injury. Sometimes, a medical device can be on the market for a long time before causing serious injuries, typically because the device somehow malfunctions.
Duty of care	A duty to use care toward patients that would be exercised by an ordinarily R-HCP, in order to protect them from unnecessary risk of harm.
Exemplary & punitive damages	<ul style="list-style-type: none"> ■ Exemplary Damages: Proper monetary compensation for the plaintiff. ■ Punitive Damages: Monetary compensation awarded to an injured party that goes beyond that, which is necessary to compensate the individual for losses and that is intended to punish the wrongdoer.
Expert witness / Expert testimony	A Juror may be unable to determine from his/her own experience if the medicine prescribed by a Physician was reasonably appropriate for a patient's illness. Experts may provide the Jury with information beyond the common knowledge of Jurors, such as scientific theories, data, tests, experiments. They establish the standard of care expected of the professional.
Fault	Departure from a standard of conduct required from a HCP by society for the protection of patients.
Fee splitting	Essentially, payment of a commission to professional colleagues, with the intention of ensuring that the referring doctor directs referrals of patients to the payee (without the knowledge of the patient).
Gross negligence	The reckless provision of health care that is clearly below the standards of accepted medical practice, either without regard to the potential consequences, or with wilful and wanton disregard to the rights and/or well-being of those for whom the duty is being performed.
Inadequate instructions or warnings	A product is defective because of inadequate instructions or warnings, when the foreseeable risk of harm posed by the product could have been reduced or avoided by the provisions of reasonable instructions or warnings.
Informed consent	Consent (provision of approval or agreement) based upon a clear appreciation and understanding of the facts, implications, and future consequences of an action.
Intervening cause	Action by a different party or entity that occurs after a defendant's negligent action and contributes to the plaintiff's injury.
Liability	The obligation that a professional practitioner has to provide care or service that meets the standard of practice of his/her specialty.
Intentional tort	Any deliberate interference with a legally recognized interest, such as the rights to bodily integrity, emotional tranquility, dominion over property, seclusion from public scrutiny, and freedom from confinement or deception.
Manufacturing defects	The product contains a manufacturing defect when the product departs from its intended design even though all possible care was exercised in the preparation and marketing of the product.

Medical devices	Health or medical instruments used in the treatment, mitigation, diagnosis or prevention of a disease or abnormal physical condition. Examples include tongue depressors, bedpans, pacemakers, in vitro diagnostic products including monoclonal antibody technology, diagnostic ultrasound products, x-ray machines and medical and surgical lasers.
Medical error	Occurs when a health-care provider chooses an inappropriate method of care or the health provider chooses the right solution of care but executes it incorrectly. Medical errors are often described as human errors in healthcare.
Medical malpractice	Improper, unskilled, or negligent treatment of a patient by a Physician, Dentist, Nurse, Pharmacist, or Other HCP.
Misrepresentation (or defectively marketed medical devices)	Any recommendation, warning (or lack of a warning), or instruction concerning the use of that medical device by a potential defendant. This category of claims involves anything from a failure to provide adequate or accurate warnings regarding the danger posed by the medical device to a failure to provide adequate instructions regarding its safe and appropriate use.
Negligence	Act or omission by a health care provider in which the treatment provided falls below the accepted standard of practice in the medical community and causes injury or death to the patient, with most cases involving medical error.
Negligence (medical products)	Liability of a medical product seller if he/she acts or fails to act in such a way as to create an unreasonable risk of harm loss to a foreseeable user using the or affected by the product in a foreseeable manner. In determining breach of duty of ordinary care, most courts use the formulation of a comparable risk-benefit model.
Party	A person or group involved in a legal proceeding as a litigant.
<i>Prima facie</i>	Evidence that, unless rebutted, would be sufficient to prove a particular proposition or fact.
Proximate cause	Event sufficiently related to a legally recognizable injury to be held to be the cause of that injury. Included in proximate cause is "causation in fact" and "foreseeability".
Quality assurance	Systematic monitoring and evaluation of the various standard aspects of a project, service or facility to maximize the probability that the outcome of the project is obtained by the production process.
Reasonable medical probability	More probable than not, not mere conjecture, that event A caused event B or will cause event C.
<i>Res ipsa loquitur</i>	(Latin for "the thing itself speaks"). Elements of duty of care and breach can be sometimes inferred from the very nature of an outcome, even without direct evidence of how any defendant behaved (facts are so obvious, a party need explain no more).
Sanction (or disciplinary action)	Action taken to punish or restrict a doctor who has demonstrated professional misconduct. Sanctions may be imposed by a state medical board, professional medical licensing organization, or the (National) Ministry of Health.
Standard of care	Formal diagnostic and treatment process that a clinician should follow for a certain type of patient, illness, set of symptoms, or clinical circumstances. It is how similarly qualified practitioners would have managed the patient's care under the same or similar circumstances. That standard will follow guidelines and protocols that experts would agree with as most appropriate, also called "best practice".
Standard (or code) of conduct	Set of conventional principles, expectations and rules that outline the responsibilities of or proper practices for an individual, party or organization.
Statute of limitations	Procedural rule that establishes a maximum period of time during which a legal suit may be initiated. After the statutory period is over, a suit cannot be initiated regardless of how strong the case may be. In the majority of legal systems, the time limit for bringing suit does not begin to run at the time of the injury, but rather when the injured person knows or should have become aware of the resulting illness or other damage. This rule found also application to late radiation injury actions.
Strict liability	Absolute legal responsibility for an injury that can be imposed on the wrongdoer without proof of carelessness or fault. This is analogous to the doctrine of " <i>res ipsa loquitur</i> ".
Strict product liability	"Automatic" responsibility (without having to prove negligence) for damages due to possession and/or use of equipment, materials or possessions which are inherently dangerous such as radioactive materials, explosives, wild animals, or assault weapons. This is analogous to the doctrine of " <i>res ipsa loquitur</i> ".
Tort	Unreasonable interference with the interests of others and for which the law permits a civil (non-criminal) action to be brought and the injured party is entitled to compensation. This may include "activities or circumstances that may cause various harms including death, bodily harm, disfigurement, disability, loss of income, loss of earning capacity, other items of financial loss or expense, damage to property, damage to reputation, alienation of affections, infliction of mental suffering, infliction of pain, or disruption of familial relationships".
Willful and wanton misconduct	Intentional wrongful conduct, done either with knowledge that serious injury to another will probably result, or with a wanton and reckless disregard of the possible results. It does not require intent to injure or harm the plaintiff individually.

Legal terms used in medical malpractice [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16].

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Abbreviated course of radiation therapy in elderly patients with glioblastoma: clinical outcome (Mansoura University)

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ABSTRACT

Background: Most patients with glioblastoma are older than 60 years, but treatment guidelines are based on trials in patients aged only up to 70 years. We did this trial to assess the impact of short schedule radiotherapy in patients aged 60 years and older with glioblastoma.

Patients & Methods: Fifty patients aged 60 years or older with a Karnofsky Performance Status (KPS) greater than or equal to 70 were treated with postoperative hypofractionated radiotherapy (34Gy administered in 3.4Gy fractions over 2 weeks). The primary endpoint of the study was overall survival. The secondary endpoints were progression-free survival, and tolerance to treatment.

Results: The median age at surgery was 71 years (range 60-81). No patient received prior or concomitant chemotherapy. At a median follow-up of 12.5 months, the median progression-free survival and overall survival were 5.8 months (95% CI, 4.1-7.9) and 10 months (95% CI, 8.9-11.1) respectively. Type of surgery (total resection vs. subtotal vs. biopsy) remained a prognostic factor ($p=0.034$). Tolerance appeared acceptable in terms of KPS changes and corticosteroid use during radiation therapy.

Conclusion: These results support the efficacy and safety of an abbreviated schedule of radiotherapy for GBM in elderly patients.

Key words: elderly patients; glioblastoma; Karnofsky performance status; radiotherapy.

INTRODUCTION

Glioblastoma (GBM) is the most common histological form of glioma and it is a typical cancer of the elderly population. The incidence peak normally occurs in individuals aged 65 years or more, and its incidence is substantially increased [1, 2].

Since the prognosis of malignant gliomas is dismal, particularly in the elderly, with the average overall survival ranging from four to eight months [3, 4, 5, 6, 18], efforts have been made to reduce the intensity and duration of the treatment for those patients in order to minimize potential toxic effects of the treatment and inconvenience associated with multiple clinic or hospital visits [7].

The value of radiotherapy in patients with poor prognosis, especially elderly patients, has been questioned. In a French trial, patients aged 70 or older who were diagnosed with glioblastoma and had a KPS of 70 or greater were randomly assigned to focal radiation therapy of

50Gy in conventional fractionation over 5.9 weeks or supportive care alone. Among the 81 patients in the analysis, those who received radiation therapy had a statistically significant improvement in median survival (29.1 weeks vs. 16.9 weeks for patients who underwent just supportive care). There was no statistically significant difference in the quality of life and cognitive function between the two groups over time [3].

Based on the results of that study, survival benefit was demonstrated with no associated toxicities with radiotherapy ($p<0.002$). However, one must consider the fact that although there was an absolute gain of 12.2 weeks in survival time, almost half of it was spent in the radiation oncology clinic for treatment [7]. Therefore, several investigators have used more abbreviated radiation therapy treatment schedules in an attempt to reduce the social and economic burden on patients and their caregivers [8, 9, 10, 11].

While the optimal regimen of radiotherapy in this fragile population remains uncertain, a Canadian randomized study found that an abbreviated course of radiotherapy, delivering a dose of 40Gy in 15 fractions, provided similar survival rates to a standard irradiation schedule (60Gy in 30 fractions) in patients aged 60 years or more with KPS greater than or equal to 50 [12]. These results prompted this review of our experience of a short course of radiotherapy in older patients suffering from GBM.

AIM OF STUDY

The aim of this study was to evaluate the impact of short schedule radiotherapy in terms of feasibility and activity, in elderly patients with glioblastoma.

PATIENTS & METHODS

Eligibility criteria

Between July 2010 and June 2012, we prospectively recruited Patients from Clinical Oncology and Nuclear Medicine Department, Mansoura University Hospital, to which patients were referred after neurosurgery.

The principal eligibility criteria included age ≥ 60 years, histologically confirmed GBM, and KPS ≥ 70 , adequate hematopoietic, renal and hepatic functions. Any of the following features rendered patients ineligible: previous cranial RT, concomitant or prior invasive cancer, and prior chemotherapy.

Pretreatment evaluation

Pretreatment evaluation included complete history, physical examination, complete blood count, blood chemistry including liver function tests, and kidney function, pre- and post-operative imaging (computed tomography and magnetic resonance imaging of the brain). Patients who fulfilled the above eligibility criteria were made aware of the purpose and the design of the study and required to sign the informed consent.

Treatment

Patients were enrolled in this prospective study to receive short-course regimen of RT (34Gy delivered in ten fractions of 3.4Gy, 5 days per week over 2 weeks). Planning target volume was calculated from dedicated CT or MRI scans of the whole brain and included the enhancing tumor with a 2cm margin, with the patient positioned in an immobilization device and in the treatment position. A multiple-field technique was used to obtain the optimum dose distribution. Supportive treatments consisted of corticosteroids at doses adjusted to the patient's clinical status. Anticonvulsants were used as medically indicated. Second-line therapy was provided at the discretion of the treating physician.

Follow-up

Patients were seen on a weekly basis during radiotherapy to monitor symptoms and toxicity. Follow-up CT and/or MRI were obtained at six weeks after completion of radiotherapy and every 3 months during the first two years of follow-up. Neuroradiographic responses criteria as defined by Macdonald *et al.* [13] were used. Tumor progression was defined as an increase in tumor size greater than 25% or presence of at least one new lesion on imaging. If progression occurred, further treatment was provided at the discretion of the treating physician. Toxicity was recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) and was recorded weekly during radiation therapy and during follow-up.

Statistical analysis

The primary endpoint of the study was overall survival. The secondary endpoints were progression-free survival, tolerance to treatment and KPS and corticosteroid doses at radiotherapy start and at completion. The Kaplan-Meier method was used to estimate survival and progression-free survival and compared using the log-rank test. Overall

Table.

Patient & tumor characteristics.

Characteristic	No.	Total %
Age (years)		
60-70	14	28
>70	36	72
Sex		
Male	32	64
Female	18	36
KPS		
70	30	60
80	14	28
90	5	10
100	1	2
Site		
Frontal	8	16
Parietal	22	44
Temporal	16	32
Occipital	4	8
Size		
<5	28	56
≥ 5	22	44
Extent of surgery		
Biopsy	16	32
Subtotal resection	32	64
Total resection	2	4

survival was defined as the interval between diagnosis and death or last follow-up. Progression-free survival was defined as the interval of time between the start of treatments and documented clinical and/or radiological disease progression after treatment. KPS and corticosteroid doses, at the start and at completion of radiotherapy, were compared using the Wilcoxon test. The Cox model was used to identify the risk factors for overall survival and progression-free survival. Prognostic factors were analyzed using the log-rank test. Multivariate analysis was done using the Cox regression, forward likelihood ratio method. Ap-value ≤ 0.05 was considered significant.

All analyses were conducted with SPSS version 15.0 (SPSS for Windows, Rel. 13.0 2004. Chicago: SPSS Inc.).

RESULTS

A. Patient's characteristics

52 patients were enrolled overall, 2 patients were excluded from all analyses: one patient died before his RT could be

started and one patient withdrew from the study and declined further treatment. 50 consecutive patients fulfilled the inclusion criteria and completed their treatment as defined in protocol.

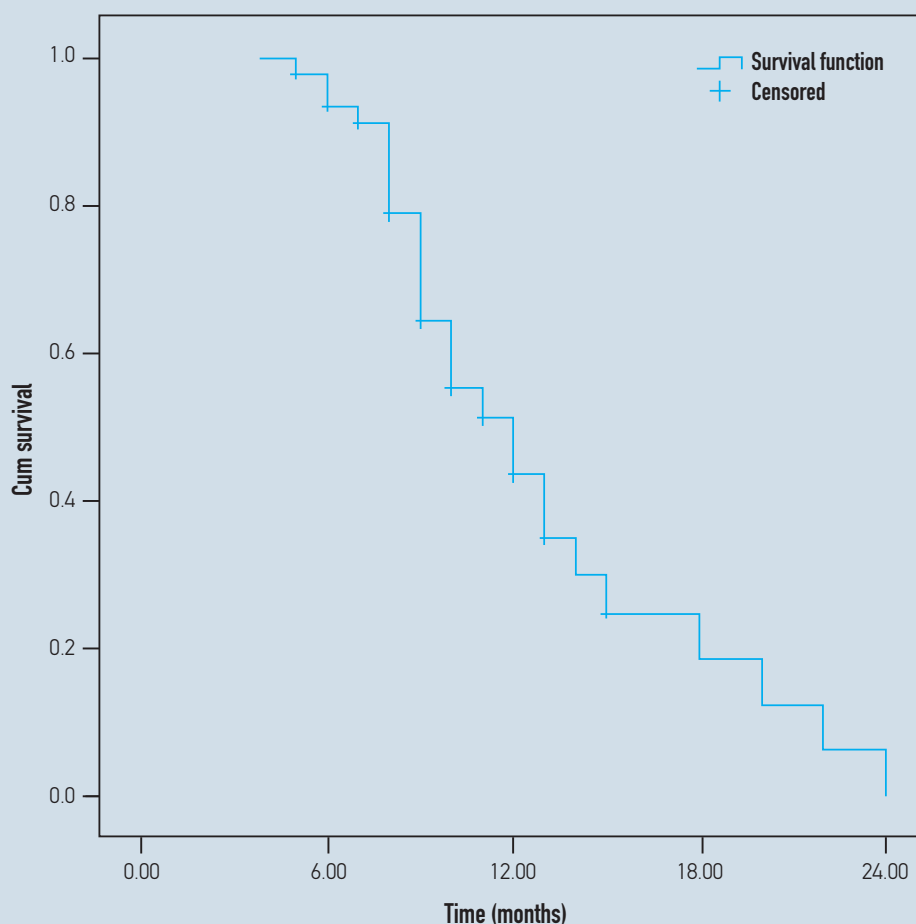
The baseline characteristics of the study patients are shown in Table. The median age of patients was 71 years (range: 60 to 81). There were 32 males and 18 females for a sex ratio of 1.8 (m/f). The median postoperative KPS was 80 (range: 70-100). 44% of patients had a parietal lesion. The tumor size was $<5\text{cm}$ in 56% of patients and 64% of patients underwent subtotal resection.

B. Regimen of radiotherapy

All patients in the study started radiotherapy, and all except four patients completed irradiation according to protocol. Of these four patients, two had deteriorated performance status. The other two patients refused to complete radiotherapy due to pulmonary infection. These four patients were included in the group for analysis.

Figure 1.

Kaplan-Meier curve of overall survival of the entire group (n=50).



C. Survival

The median follow-up period was 12.5 months (95% CI: 8-17.5) and no patient was lost to follow-up. The median progression-free survival and overall survival were 5.8 months (95% CI, 4.1-7.9) and 10 months (95% CI, 8.9-11.1), respectively (Figures 1, 2). The actuarial overall survival rates at 6 and 12 months were 83.6% and 24%, respectively (Figure 1). At the time of data analysis, 18 patients died: 15 of tumor progression, 2 of pulmonary infection and one of another cause. Multivariate analysis on all patients ($n=46$) showed prognostic value for surgery (biopsy vs. subtotal vs. total excision, $p=0.034$).

D. Evolution of the KPS and corticosteroid uptake during radiotherapy

The KPS did not change between the postoperative period (median KPS = 70) and the end of radiotherapy (median KPS = 70). Corticosteroid use was not significantly different between the beginning and the completion of radiation therapy

($p=0.931$). Twelve (24%) of 50 patients required a post-treatment increase in total daily dose of corticosteroids from beginning of treatment. Complications of corticosteroid treatment included diabetes in two patients and myopathy in three patients.

E. Chemotherapy

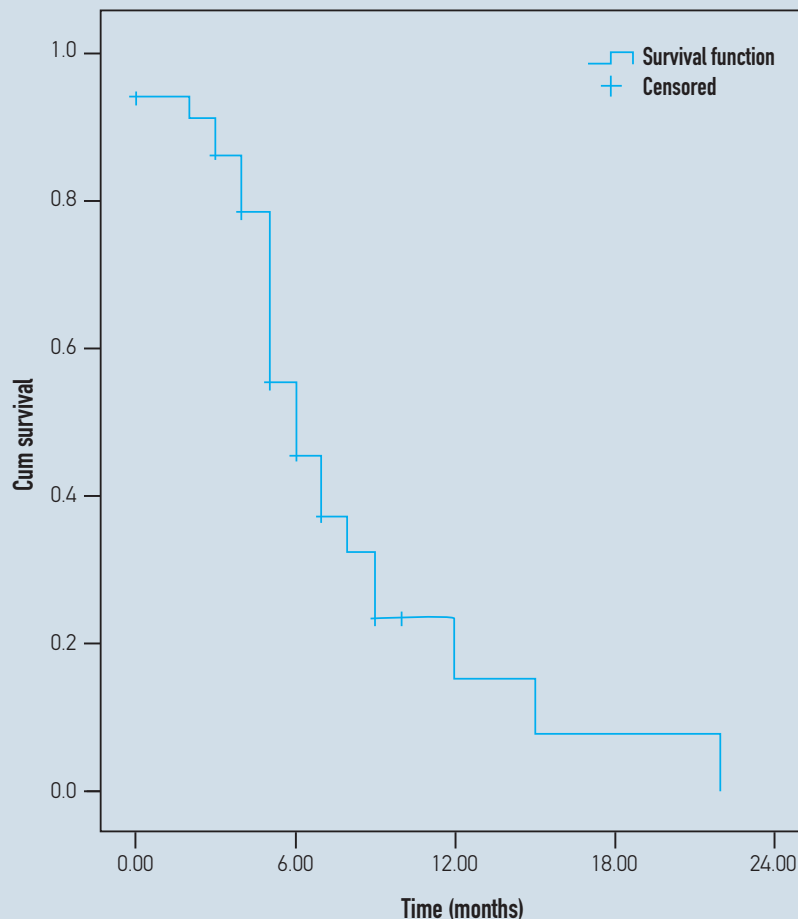
Second-line treatment was given to 15 (30%) of the 46 patients who completed radiotherapy; twelve patients received one line of chemotherapy; and three patients received two lines of chemotherapy.

F. Treatment safety

Radiotherapy was well-tolerated in most patients and could be completed without interruption in 92% of patients; nine patients (18%) experienced neurological toxicity during or immediately at the end of radiotherapy, mainly confusion

Figure 2.

Kaplan-Meier curve of progression-free survival of the entire group ($n=50$).



and/or somnolence. Symptoms were reversible in all patients following an increase of steroid dose. Only 2 (4%) patients developed late toxicity in the form of radiation-induced MRI encephalomalacia that signifies irreversible vascular effect, and may lead to progressive cognitive decline. No other toxicities were observed.

DISCUSSION

Chemoradiotherapy with temozolomide became the standard of care for patients with glioblastoma in 2004, but its introduction was based on a pivotal study in which patients were aged 70 years or younger; increasing age was found to be a negative prognostic factor [14]. Elderly and frail patients might, therefore, not be viewed as candidates for combined therapy, and extensive treatment might not be seen as justifiable owing to the short survival [15]. Alternatives to the standard 6 weeks of radiotherapy that are associated with similar or improved survival and quality of life would be beneficial. In our locality, many factors must be considered when treating these patients; age group is not equivalent to its respective one in another country due to poor nutrition and ignorance, unavailability of costly chemotherapy due to limited resources, and large number of patients being unable to complete the planned a 6-week standard radiotherapy regimen, which seems to be associated with substantial risks of morbidity and early discontinuation. In this setting of a rapidly fatal illness, patients and families will be especially attuned to treatments and management strategies that preserve and respect their quality of life. Judging by our own experience, measuring this important outcome in older patients with GBM may prove to be a significant research challenge.

In our study the median OS was 10 months, which is in accordance with previously reported prospective trials in elderly patients with glioblastoma; Hoegler and Davey [16] evaluated radiotherapy delivering 37.5Gy in 15 daily fractions in patients aged 70 years or older with high-grade astrocytomas, mainly GBM. Among the 25 patients included, 12 patients with a KPS above 70 had a median OS of 10.4 months. Pierga *et al.* [17] reported a median OS of 10 months in patients aged 70 years or older with high-grade glioma and a KPS greater than or equal to 70 who underwent radiation therapy delivering 45Gy in 25 fractions.

In contrast, the median OS observed in our series (10 months) is slightly inferior to those previously reported using a short course of radiotherapy by Idbaih *et al.* [18], who investigated the efficacy of short schedule radiotherapy (40Gy in 15 fractions) for GBM in 28 elderly patients with a good KPS and found a median survival of 11.8 months. In this study, chemotherapy, which was administered after radia-

tion therapy in 55% of their patients, may partially explain this difference.

Recently, the Nordic randomized, phase 3 trial of hypofractionated radiotherapy versus standard radiotherapy versus temozolomide in patients older than 60 years with glioblastoma [19] reported worse outcomes with standard radiotherapy than with temozolomide or hypofractionated radiotherapy and suggested that temozolomide alone or hypofractionated radiotherapy over 2 weeks might be valid alternative strategies. Median survival for those who received 34Gy radiotherapy was 7.5 months (95% CI 6.5-8.6), whereas in this study it was 10 months (95% CI 8.9-11.1). This difference might be explained by the small number of patients included in the present series.

The potential role of surgery is questioned in the elderly. In this study, the extent of surgery had impact in terms of OS when biopsy was compared with partial or complete resection. This result is in accordance with Pierga *et al.* [17], and Kelly and Hunt [4], who suggested a benefit of surgical resection. In contrast, Hoegler and Davey [16] reported that the extent of surgery had no impact in terms of OS. A randomized study by Vuorinen *et al.* [20] concluded that there was a modest impact of surgery versus biopsy ($p=0.04$) in patients aged 65 years or older with malignant glioma.

Only 4% of patients developed late toxicity, which is supported by results obtained from a retrospective study by the University of Texas M.D. Anderson Cancer Center [9]: 59 patients with glioblastoma who were elderly or younger but with poor performance status were treated with a hypofractionated radiotherapy regimen of 50Gy in 20 fractions. Only three cases (5.1%) of radiation necrosis were observed. Furthermore, Slotmann *et al.* [21] and Hulshof *et al.* [22] reported no acute or late toxicities.

New radiotherapy strategies are being developed against GBM and give promising results [23, 24, 25, 26]. These approaches also constitute a hope in elderly patients suffering from GBM.

This trial has some limitations. One is the relatively small number of patients. Another factor is that it is a single institution study. Multicenter randomized trials are necessary to clarify the role of abbreviated course of radiation therapy in elderly patients with GBM.

Our trial confirms that the overall prognosis for elderly patients with glioblastoma is poor. We found that short-term radiotherapy is a potential alternative option for older patients with GBM due to decrease increment in corticosteroid requirement, and reduced treatment time.

Conflict of interest statement

The authors declare no conflict of interest.

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Developments in the treatment of locally advanced cervical cancer

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ABSTRACT

Despite the available prevention and early detection strategies, squamous-cell carcinoma of the uterine cervix is still diagnosed as locally advanced disease in a large proportion of patients. Treatment with cisplatin, in combination with external beam irradiation, has been the cornerstone of treatment in this setting for more than two decades. Induction chemotherapy strategies followed by concurrent chemo-radiation or surgery and pre-operative concurrent chemo-radiation have been recently implemented in clinical trials in an effort to optimize both local control and the occurrence of distant metastases. More recently, combinations of chemotherapy or radiotherapy with molecular agents targeting critical pathways in cervical malignant transformation are being assessed in clinical trials. In this paper, we review the role of cisplatin in the disease in the context of other potent radiosensitizers. We also discuss all recently implemented therapeutic modalities for the treatment of locally advanced cervical cancer with emphasis on the novel induction strategies. Concerns regarding treatment-related toxicity in the context of co-morbidities and the need for potent predictive biomarkers for individualized therapeutic approach are also addressed.

Key words: cervical cancer; locally advanced; chemotherapy; radiotherapy; toxicity; prognostic and predictive markers.

INTRODUCTION

Squamous carcinoma of the uterine cervix, often referred to as cervical cancer, remains a major concern for public health. Worldwide, cervical cancer accounted for 287,000 deaths in 2008, and the number is expected to rise up to 410,000 by 2030 [1, 2]. Despite the worldwide implementation of prevention and early detection strategies, including the Papanicolaou smear test, human papillomavirus (HPV) testing and vaccines, approximately 30% of newly diagnosed cases still fall into the category of "locally advanced disease", indicating tumor spreading outside the uterine cervix at the time of diagnosis [3]. Moreover, 50% of patients with locally advanced disease are expected to relapse within the first 2 years from initial treatment [4].

Cisplatin monotherapy, often combined with external-beam irradiation, remained the dominant treatment for locally advanced disease for more than fifteen years [5]. More recently, induction chemotherapy strategies followed by concurrent chemo-radiation or surgery and

pre-operative concurrent chemo-radiation have been recently implemented in clinical trials in an effort to optimize local control and at the same time minimize the risk for metastatic disease. In this review, we discuss established and developing therapeutic approaches in the management of locally advanced cervical cancer, focusing on novel strategies combining induction treatments with surgery or concurrent chemo-radiotherapy. Special emphasis is given on toxicity issues, the incorporation of newer biological agents in the therapeutic armamentarium and the potential utility of predictive and prognostic markers.

CONCURRENT CHEMO-RADIATION BASED ON PLATINUM-CONTAINING REGIMENS

Radiation alone fails to control disease in over 35% of patients with cervical cancer diagnosed at *Fédération Internationale de Gynécologie et d'Obstétrique* (FIGO) stages IB2-IVA [6]. Five-year survival rates up to 72.2%, 63.7%, 41.7% and 16.4% for stages IB2, IIB, IIIB and IVA, respectively, have been reported with exclu-

sive radiation [7]. Concurrent chemo-radiation has led to a significant benefit in reducing both local and distant recurrences in five randomized studies [8, 9, 10, 11, 12] that involved a total of 1,894 women. In the trial conducted by the Radiotherapy Oncology Group (RTOG), Morris *et al.* [14] randomized 401 stage IB-IVA patients to either concurrent chemo-radiation with cisplatin and 5-fluorouracil (5-FU) or to extended-field radiation alone (control group). Concurrent chemo-radiotherapy resulted in an overall survival rate of 73% compared to 58% for radiation alone and also decreased the rates for both local and distant recurrences. In another prospective phase III multicenter randomized trial reported at the same time with the former, Rose *et al.* [13] recruited 526 evaluable patients with stage IIB-IVA cervical cancer in a Gynecologic Oncology Group (GOG) three-arm trial that compared weekly cisplatin versus cisplatin, 5-FU and hydroxyurea versus hydroxyurea alone, concurrently with radiation therapy. Superior survival rates for both cisplatin-containing regimens (66% and 64%, respectively) compared with hydroxyurea alone (39%) were reported [13].

Cisplatin as a potent radiosensitizer has been extensively evaluated and has been proven superior to hydroxyurea [12] and less toxic than the cisplatin/5-FU/hydroxyurea combination [13]. Whitney *et al.* [12] randomized 388 patients with stage IIB-IVA disease in a Gynecologic Oncology Group (GOG) trial to receive either radiation therapy with concurrent cisplatin and 5-FU or hydroxyurea. Patients in the cisplatin arm had a significantly better 5-year survival rate (63% versus 47%). In a meta-analysis based on 19 trials (including a total of 4,580 patients), an absolute survival benefit of 12% at 5 years with concurrent chemo-radiation based on cisplatin as compared to radiation alone was demonstrated [13]. An update of the same work comprising 24 trials involving 4,921 patients showed that chemo-radiation improves both overall survival (OS) and progression-free survival (PFS), when a platinum compound was used, with an absolute benefit of 10% [14]. Importantly, in a pilot study conducted by Nugent *et al.* [15], the number of cisplatin chemotherapy cycles was independently predictive for PFS and OS. Patients who received less than six cycles had worse clinical outcome as compared to those who completed at least six cycles of treatment. Regarding the optimal dosing, a randomized trial comparing cisplatin at 40mg/m² weekly with cisplatin at 75mg/m² every 3 weeks, reported twice as many delays of therapy with the higher, less frequent cisplatin administration [16]. On the ground of available evidence regarding clinical efficacy and acceptable tolerance, weekly cisplatin at the dose of 40mg/m² is considered the standard regimen that other agents should be compared to [17].

Although carboplatin may also serve as an active radiosensitizer [18-22] and is less toxic than cisplatin in patients with renal dysfunction due to ureteral obstruction, efficacy results from phase I-II trials are generally modest and objective response rates (ORR) are inferior to those reported

with cisplatin [19-23]. Multiple combinations that incorporated carboplatin have been evaluated, with the combination of docetaxel with carboplatin exhibiting encouraging results [20, 21]. The weekly paclitaxel and carboplatin chemo-radiation regimen has been also proven feasible and active in phase I trials [22, 23], yet dose-limiting diarrhea makes this regimen poorly tolerated [24]. Concurrent chemo-radiation with tegafur-uracil (UFT) and carboplatin showed no difference in respect to ORR, PFS, OS and treatment-related toxicity as compared to carboplatin alone in a prospective, phase III trial that recruited 469 patients with stage IIB-IIIB cervical cancer [25]. Finally, in a case-control study, the combination of radiotherapy, concurrently with 5-FU and carboplatin, has been compared to radiation alone in the same setting. The authors reported similar ORR, DFS and OS between the two groups of patients. Acute toxicity, primarily hematological, was significantly higher in the cases than in the controls (25% vs. 3%) [26].

Since 5-FU represents a potent radiosensitizer too, a number of studies have been undertaken to clarify the use of both agents in combination with pelvic radiotherapy. In a study by Kim *et al.* [27], 158 patients with FIGO stage IIB through IVA disease were assigned to either monthly 5-FU and cisplatin or weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy. The response rate for each group was 91%. Four-year OS and PFS rates were 70% and 67%, respectively, with the combination regimen, while with weekly cisplatin they were 67% and 66%, respectively. The authors concluded that chemo-radiation with weekly cisplatin significantly improved compliance with treatment and reduced acute hematological toxicity without affecting response and survival rates compared to the combination arm. Another trial designed to compare protracted venous infusion (PVI) of 5-FU with standard weekly cisplatin and concurrent RT in patients with stage IIB, IIIB, and IVA cervical cancer was prematurely terminated when a planned interim analysis indicated that the PVI 5-FU/RT treatment arm had a higher treatment failure rate (35% higher) and would, most likely, not result in any improvement in PFS compared with weekly cisplatin/RT [28]. Yet clinical interest in 5-FU and its combinations is still active: Recently, in a study that re-evaluated the efficacy of concurrent chemo-radiation using 5-FU and cisplatin in 57 patients with stage IIB-IVA and bulky IB2-IIA tumors, an ORR of 91.5% with a 5-year OS and a 3-year PFS rate of 69.4% and 74.9%, respectively, were reported [29]. In the same context, another study compared survival outcomes and toxicities between concurrent chemo-radiotherapy with cisplatin plus 5-FU and cisplatin plus paclitaxel in 93 patients with locally advanced cervical carcinoma. No significant differences were found in 5-year DFS or OS between the two treatment groups. Nevertheless, the cisplatin plus paclitaxel arm was associated with increased leukopenia, neutropenia and peripheral neuropathy, but less gastrointestinal toxicity (nausea) compared to the cisplatin plus 5-FU arm [30].

Capecitabine, an oral pro-drug of 5-FU, has also been evaluated in the same setting with promising results. In a phase I study of daily capecitabine combined with weekly cisplatin and radiotherapy, a PFS at 12 months of 69.2%, and at 24 months of 49.2%, with an OS rate of 57.7% at 24 months were reported [31]. Following these results, a phase II study evaluated 60 patients with stage IIB-IIIb disease that received capecitabine during radiation, followed by six cycles of capecitabine monotherapy. The ORR was 88%, while the 1-year PFS and OS rates were 86% and 95%, respectively. At 23 months, 76% of patients were progression-free and complete response (CR) was maintained in 90% of the 48 patients who originally achieved a CR [32].

In a pilot phase II study designed to investigate the feasibility, efficacy, and safety of gemcitabine in combination with irradiation in 19 chemo-naïve patients with FIGO stage IIB cervical cancer, a CR was observed among 17 (89.5%) of them and after a median follow-up time of 19.9 months, all patients were alive with sixteen of them remaining relapse-free [33]. On these grounds, the gemcitabine-cisplatin combination was administered concurrently with radiotherapy in a phase I/II study resulting in a 97.3% ORR (88.8% were complete responses). The 3-year RFS and OS rates were estimated to 67% and 72%, respectively [34]. These encouraging results led to a large randomized, phase III trial designed to determine whether the addition of gemcitabine to concurrent cisplatin chemo-radiotherapy could improve outcome compared with current standard of care in locally advanced cervical cancer: Five hundred and fifteen patients with stage IIB-IVA disease were randomly assigned to either cisplatin and gemcitabine, weekly for 6 weeks with concurrent external-beam radiotherapy, followed by brachytherapy and then two adjuvant cycles of cisplatin plus gemcitabine, (arm A) or to cisplatin and concurrent radiotherapy followed by brachytherapy only at the same doses (arm B). PFS at 3 years was significantly improved in arm A versus arm B (74.4% versus 65.0%, respectively; $p=0.029$), as were overall PFS (hazard ratio [HR]=0.68; 95% CI, 0.49 to 0.95; $p=0.0227$) and OS (HR=0.68; 95% CI, 0.49 to 0.95; $p=0.0224$). The authors concluded that gemcitabine plus cisplatin chemo-radiotherapy followed by brachytherapy and adjuvant gemcitabine/cisplatin chemotherapy improved survival outcomes with increased but clinically manageable toxicity when compared with standard treatment [35]. Although these results challenge the current standard of cisplatin monotherapy, since patients in the experimental arm also received two cycles of adjuvant chemotherapy, it is not clear to what extent the survival benefit observed in the experimental arm is attributable to the addition of gemcitabine in the chemo-radiation phase or to the addition of an adjuvant chemotherapy phase itself.

Nedaplatin is a synthetic analog of cisplatin that exhibits less nephrotoxicity, neurotoxicity and gastrointestinal toxicity. Weekly nedaplatin concurrently with radiation achieved an ORR of 90%, a 3-year PFS of 58.7% and an OS of 78.0% in a pilot phase II trial [36]. In a following randomized phase II

study nedaplatin-based concurrent chemo-radiotherapy showed superior clinical efficacy and no statistically significant difference in toxicity as compared to radiotherapy alone [37]. Multiple combinations incorporating nedaplatin have also been evaluated, mainly in phase I trials. The combination of paclitaxel and nedaplatin concurrently with radiotherapy, followed by consolidation treatment with the same regimen resulted in a CR of 88% and an estimated 2-year PFS and OS rate of 82% and 93%, respectively [38].

CONCURRENT CHEMO-RADIATION BASED ON NON PLATINUM-CONTAINING REGIMENS

Among taxanes, paclitaxel has been extensively evaluated within chemo-radiation regimens. The feasibility of concurrent radiotherapy and paclitaxel was evaluated in a pilot study with 20 patients (13 new cases, stage IIB-III, and 7 with pelvic recurrences) and complete regression was reported in 63% [39]. In a subsequent randomized phase II trial, weekly cisplatin was compared to weekly paclitaxel as concurrent chemotherapy with standard RT in patients with stage IB2-IVA disease or with post-surgical pelvic recurrence: The proportion of patients surviving at 2 and 5 years was 78% and 54% for the cisplatin arm and 73% and 43% for the paclitaxel arm, respectively, thus suggesting that weekly paclitaxel does not provide any clinical advantage over weekly cisplatin [40]. A multi-agent regimen that included paclitaxel, ifosfamide and cisplatin (TIP) has been also evaluated in two different settings, bulky and locally advanced cervical cancer and recurrent-persistent disease in a total of 38 patients: Eleven women achieved a clinical CR, 21 had a partial response and only one patient had progressive disease (PD), accounting for an impressive ORR of 84.2% [41]. Finally, the combination of paclitaxel and vinorelbine was associated with significant hematological toxicity [42].

Mitomycin C is a drug that has been extensively evaluated in the locally advanced cervical cancer setting. In an earlier study, 40 patients with stage IB-IVA disease received mitomycin C and 5-FU followed by sequential pelvic irradiation: A complete response rate of 63%, a local control rate of 58% and a 5-year survival rate of 44% were obtained which were not superior to those achieved with radiation alone [43]. Another larger trial randomized 160 patients with locally advanced disease to receive either RT alone or RT with concomitant mitomycin C: The four-year DFS rates for RT with mitomycin C and RT alone were significantly different (71% versus 44%) [44]. Using a combination regimen of 5-FU with mitomycin C and radiotherapy, Ludgate *et al.* suggested an improvement in pelvic control and in the 3-year survival rate for the combined modality compared to RT alone (55% versus 28%) using, however, historical controls with remarkably low response rates as a reference [45]. Similar results were obtained in another study using the same combination concurrently with RT, although the authors commented that the regimen failed to control distant metastasis in late-stage patients [46]. In a pilot trial, 60 women with advanced cervical

cancer were treated with a combination of external and intracavitary RT along with one cycle of 5-FU and mitomycin C and a second cycle of 5-FU and cisplatin. The 5-year OS for stage IIB and IIIA-IVA patients was 48% and 39%, respectively [47]. Christie *et al.* reviewed 177 patients treated with pelvic radiotherapy for locally advanced disease and focused on 93 patients who had received chemotherapy with infusional 5-FU with or without bolus mitomycin C. The median OS for all patients was 47 months, but was significantly higher (87 months) for the combination regimen group. Rates of PFS and local control were also higher in the same group, at the cost of substantial toxicity, with 36% of patients in the combination arm experiencing grade 3 or 4 complications [48]. Finally, in a phase II trial, women with FIGO stage IIB-IVA disease who received cisplatin, 5-FU, mitomycin C and concomitant radiotherapy achieved an ORR of 82%. All patients developed acute hematological toxicity and two patients experienced severe late bowel toxicity. The lack of clinical efficacy improvement compared to historical controls treated with cisplatin alone and the late bowel toxicity discouraged further use of that regimen [49].

Topotecan and irinotecan are topoisomerase II inhibitors that have been evaluated in combination with RT in locally advanced cervical cancer. The feasibility of adding weekly topotecan to cisplatin in 12 patients with stage IB2-IVA disease receiving pelvic irradiation has been affirmed in a pilot trial and responses up to 92% were reported [50]. The safety and feasibility of concurrent radiation therapy and weekly irinotecan in patients with locally advanced disease was also affirmed in two small phase II trials, showing promising efficacy and mostly tolerable adverse events [51, 52]. However, further and larger studies will be required in order to clarify the exact role of camptothecins in combination with RT in the locally advanced setting of cervical cancer.

NEOADJUVANT CHEMOTHERAPY OR CHEMO-RADIOTHERAPY

Neoadjuvant or induction chemotherapy has been increasingly evaluated in the locally advanced setting in an effort to optimize local control and, at the same time, to prevent early systemic dissemination of the disease. Early studies on neoadjuvant chemotherapy suggested that responders who underwent surgery may obtain clinical benefit over radiotherapy alone [53]. In 1990, a phase III trial was undertaken to examine the efficacy of neoadjuvant chemotherapy, recruiting 441 patients with stage IB2 to III cervical cancer who were randomly allocated to receive either cisplatin-based neoadjuvant chemotherapy followed by radical surgery (arm A) or external-beam RT followed by brachytherapy (arm B). Five-year DFS rates of 55.4% and 41.3% and 5-year OS rates of 58.9% and 44.5% were observed for arms A and B, respectively, and these differences were statistically significant (DFS: $p=0.02$; OS: $p=0.007$) [54]. A subsequent randomized trial on 106 women with stage IB cervical cancer assigned them to receive either neoadjuvant chemotherapy or primary sur-

gery alone. The overall clinical response rate after neoadjuvant chemotherapy was 84.6%, including complete responses in 7.7% of patients. Interestingly, surgery revealed positive lymph nodes in 9.6% of patients in the neoadjuvant chemotherapy group and in 29.6% of patients in the primary surgery group ($p=0.014$). The overall 5-year survival rate was significantly higher for patients who received neoadjuvant chemotherapy (84.6%) than for those in the control group (75.9%) ($p=0.0112$). Furthermore, the median survival time in patients with complete or partial response to chemotherapy was significantly higher than that of patients with stable disease after chemotherapy (83.3 versus 55.2 months, $p=0.0049$) [55]. Similar results were reported in another study addressing the same question in patients with bulky stage IB-IIA disease [56], although these reports were challenged by a subsequent negative study [57]. The crucial role of lymph node involvement after neoadjuvant treatment was pointed out by a retrospective study that compared preoperative chemo-radiation to neoadjuvant chemotherapy in 127 patients with locally advanced cervical cancer: Metastatic pelvic lymph node involvement was significantly lower in the neoadjuvant chemo-radiotherapy group as compared to the neoadjuvant chemotherapy group (11.5% versus 30.0%, $p=0.009$) [58]. The feasibility of post-operative radiotherapy following either neoadjuvant radiotherapy or neoadjuvant chemotherapy has been also explored [59].

Neoadjuvant chemotherapy for locally advanced disease possesses the theoretical disadvantages of a delay of curative treatment, such as surgical resection, for non-responders, as well as the development of potentially radio-resistant cancer cells. A pilot study [62] attempted to overcome these drawbacks by using a "quick" high-dose chemotherapy scheme administered over a short period of time before surgery. In this randomized trial, 142 patients with stage IB2-IIIB disease were assigned to receive either modified neoadjuvant chemotherapy followed by surgery or primary surgery directly (control arm). Histopathological findings after surgery showed that pelvic lymph node metastasis and parametrial infiltration rates were significantly lower in the neoadjuvant chemotherapy group as compared to the primary surgery group ($p=0.025$ and 0.038 , respectively). Among patients in the experimental arm, the lymph node metastasis rate was still as high as 45.5% in non-responders to neoadjuvant chemotherapy, but declined to 16.0% in responders ($p=0.008$). Although neoadjuvant chemotherapy was associated with a marginal survival benefit over surgery alone ($p=0.041$), multivariate analysis did not indicate the type of therapeutic modality as an independent prognostic factor. However, response to neoadjuvant chemotherapy was an independent predictor of survival in the same setting ($p=0.005$) [60]. The subsequent incorporation of taxanes in the therapeutic armamentarium led to another randomized trial where authors tested the hypothesis that neoadjuvant chemotherapy with paclitaxel plus platinum may improve clinical outcomes and spare toxicity from adjuvant radiotherapy in patients with stage IB2-IIA bulky cervical cancer. As expected,

in the neoadjuvant chemotherapy group, pathological tumor size was significantly smaller and fewer patients had deep cervical invasion. Nevertheless, radiotherapy, either alone or in the form of concurrent chemo-radiation, was administered to more patients treated with radical surgery alone (82.9% versus 52.9%, $p=0.006$). Again, there were no significant differences in 5-year DFS and OS [61]. Recently published data [64] regarding long-term follow-up of women with locally advanced cervical cancer who had received neoadjuvant chemotherapy supports the previous observations: No differences were demonstrated regarding DFS and OS (65.4% versus 53.5% and 70.4% versus 65.9%, respectively) among 288 women with stage IB-IIIB disease who were randomized to receive either neoadjuvant cisplatin, vincristine and bleomycin chemotherapy followed by surgery or exclusive radiotherapy [62]. Another retrospective study compared the long-term survival of 476 patients with original stage IB2-IIIB disease treated with neoadjuvant chemotherapy followed by radical hysterectomy to a mixed control group comprising radical surgery and concurrent radical chemo-radiotherapy: The analysis indicated that neoadjuvant chemotherapy improved the long-term DFS and OS as compared to the control arm and especially compared to the concurrent chemo-radiotherapy group. Of note, patients receiving paclitaxel and cisplatin, as neoadjuvant treatment, had a statistically significant improvement in both 5-year DFS and OS rates ($p<0.001$ for both comparisons) [63]. Finally, in a recent retrospective study, a total of 120 patients with initial stage IB2-IIIB cervical cancer received either 2 cycles of neoadjuvant chemotherapy with irinotecan plus cisplatin followed by surgery or were directly operated. After a median follow-up of 30 months, the intra-pelvic recurrence rate of the neoadjuvant chemotherapy group was significantly lower than that of the control group (3/60 versus 11/60, $p=0.023$), while the 2-year PFS and the 2-year OS did not differ significantly between the two groups. Multivariate analysis showed that response to neoadjuvant chemotherapy was once again the only factor associated with improved survival ($p=0.036$) [64]. A recently published Cochrane-base systematic review and meta-analysis attempted to clarify the landscape by assessing the

role of neoadjuvant chemotherapy in women with early or locally advanced cervical cancer including 6 randomized controlled trials involving 1,072 women. Exploratory analyses of pathological response showed a significant decrease in adverse pathological findings with neoadjuvant chemotherapy (HR=0.54, 95% CI=0.39 to 0.73, $p<0.0001$ for lymph node status; HR=0.58, 95% CI=0.41 to 0.82, $p=0.002$ for parametrial infiltration) which despite a high level of heterogeneity was still significant when the random effects model was used [65]. While PFS was significantly improved with neoadjuvant chemotherapy (HR=0.76, 95% CI=0.62 to 0.94, $p=0.01$), no significant OS benefit was observed (HR=0.85, 95% CI=0.67 to 1.07, $p=0.17$). Furthermore, estimates for both local (HR=0.76, 95% CI=0.49 to 1.17, $p=0.21$) and distant (HR=0.68, 95% CI=0.41 to 1.13, $p=0.13$) recurrence only tended to be in favor of neoadjuvant chemotherapy.

REGIMENS EVALUATED IN THE NEOADJUVANT SETTING

Initial neoadjuvant chemotherapy strategies in locally advanced cervical cancer involved short-term cisplatin monotherapy regimens [66]. The triplet chemotherapy regimen with cisplatin, bleomycin, and methotrexate was one of the first combinations evaluated, that achieved an overall response rate of 75.7%, including cases of initially bulky tumors [67]. Similar response rates were obtained with other therapeutic combinations, such as cisplatin, vincristine and bleomycin [68] or cisplatin with bleomycin [69]. The so called PVB regimen (cisplatin, vinblastine and bleomycin) led to reduction of tumor size in 93.7% of patients in another study: Overall 5-year and 10-year PFS rates were 82 and 79.4%, respectively [70]. Besides the previously mentioned studies a significant number of other phase II trials have evaluated numerous doublet and triplet platinum and non-platinum combinations, implementing among others bleomycin [71], mitomycin-C [72, 86, 89], vinblastine [73], pirarubicin [74], ifosfamide [75, 76], vinorelbine [77, 78], 5-fluourouracil [79, 80, 81], gemcitabine [82], paclitaxel [83, 84, 85, 86], docetaxel [87], irinotecan [66, 88, 89, 90, 91], topotecan [92], etoposide [93] and epirubicin [94]. The main characteristics of these trials are summarized in Table 1.

Table 1.
Main phase II trials of induction chemotherapy in locally advanced cervical cancer.

Trial	Year	Regimen	N	FIGO stage	ORR%	Remarks
Weiner SA <i>et al.</i> [73]	1988	Mitomycin C Vincristine Bleomycin Cisplatin	20	Locally advanced	72.1	Prior to radiotherapy of curative intent
Deppe G <i>et al.</i> [74]	1991	Mitomycin C Cisplatin	17	IB-IIIB	76.5	Prior to radical hysterectomy or radiotherapy

Trial	Year	Regimen	N	FIGO stage	ORR%	Remarks
Aoki Y <i>et al.</i> [75]	2001	Cisplatin Vinblastine Peplomycin	21	IB-IIB	86	84% 5-year overall survival
Terai Y <i>et al.</i> [76]	2009	Cisplatin Mitomycin C Pirarubicin	60	IIB-IVA	96.7	Neoadjuvant intra-arterial chemotherapy
Zanetta G <i>et al.</i> [77]	1997	Cisplatin Ifosfamide Paclitaxel	38	IB2-IVA	34	
Kumar JV <i>et al.</i> [78]	2009	Cisplatin Ifosfamide Paclitaxel	56	IB-IVA	87.5	Retrospective cohort
Mastroianni <i>et al.</i> [79]	2000	Cisplatin Vinorelbine		IB-IVA	90	
Di Vagno G <i>et al.</i> [80]	2003	Cisplatin Vinorelbine	58	IB-IVA	85	81% were submitted to radical surgery
Etcheverry MG <i>et al.</i> [81]	2000	Cisplatin 5-fluorouracil Ifosfamide	53	IB2-IIIB	85	Prior to radical hysterectomy or radiotherapy
Mariagrazia D <i>et al.</i> [82]	2005	Cisplatin 5-fluorouracil	100	IB-IVA	96	Concurrent radiotherapy
Shibata K <i>et al.</i> [83]	2009	Cisplatin 5-fluorouracil	25	IB2-IVA	96	Concurrent radiotherapy. Cisplatin administered intra-arterially or intravenously
Duenas-Gonzalez A <i>et al.</i> [84]	2001	Cisplatin Gemcitabine	41	IB2-IIIB	95	23 patients underwent radical surgery
D'Agostino G <i>et al.</i> [85]	2002	Cisplatin Epirubicin Paclitaxel	42	IB2-IVA	78.5	76.2% of patients underwent radical surgery
Duenas-Gonzalez A <i>et al.</i> [86]	2003	Paclitaxel Carboplatin	43	IB2-IIIB	95	Adjuvant radiation concurrent with 6-weekly doses of cisplatin
Benedetti-Panici P <i>et al.</i> [87]	2007	Paclitaxel Cisplatin	18	IVA	67	
Mori T <i>et al.</i> [88]	2008	Paclitaxel Carboplatin	30	IB2-IVA	87	Weekly schedule of neoadjuvant chemotherapy
Kokawa K <i>et al.</i> [90]	2007	Irinotecan Mitomycin C	33	IB-IVA	85.7	Median survival: 44 months
Sugiyama T <i>et al.</i> [91]	1999	Cisplatin Irinotecan	23	IB2-IIIB	78	
Raspagliesi F <i>et al.</i> [92]	2010	Cisplatin Irinotecan	87	IB-IVA	73.2	4-year survival: 87%
Ying X <i>et al.</i> [66]	2011	Cisplatin Irinotecan	60	IB2-IIB	65	
Ren Y <i>et al.</i> [93]	2011	Cisplatin Irinotecan	52	IB-IVA	78.8	Retrospective cohort
Manci N <i>et al.</i> [94]	2011	Cisplatin Topotecan	46	IB2-IIIB	89.5	2-year survival: 81%
Huang X <i>et al.</i> [89]	2011	Docetaxel Cisplatin	52	IB2-IIB	86.5	Retrospective cohort
Bae JH <i>et al.</i> [95]	2008	Cisplatin Etoposide	99	IB-IIB	69.7	5-year survival: 88.1%

FIGO: International Federation of Gynecology and Obstetrics

EVALUATION OF RESPONSE TO NEOADJUVANT THERAPY AND CLINICAL BENEFIT

Multiple clinical and biological parameters have been evaluated in patients with locally advanced cervical cancer in an effort to consistently and reproducibly predict response to neoadjuvant chemotherapy. In one of several studies which evaluated neoadjuvant chemotherapy containing cisplatin, bleomycin plus/minus methotrexate followed by radical hysterectomy in 130 patients with stage IB2-III cervical cancer, logistic regression analysis demonstrated that FIGO stage, cervical tumor size, parametrial involvement and histological type are highly predictive of response and clinical benefit from neoadjuvant chemotherapy: The 10-year survival estimates were 91%, 80% and 34.5% for stages IB2-IIA, IIB and III, respectively ($p < 0.001$). The 10-year DFS estimates were 91% and 44% for stage IB2-IIB and III, respectively ($p < 0.001$) [95]. In a similar manner, a second study among 75 patients with stage IB-III disease who had received three courses of neoadjuvant chemotherapy including cisplatin, bleomycin and methotrexate showed significantly lower response rates in patients with tumor size $> 5\text{cm}$ in diameter and bilateral parametrial involvement to the pelvic side wall. Patients achieving CR or PR had a significantly improved 3-year survival rate compared with those who did not. Pathological parametrial involvement and cervical infiltration $\geq 5\text{mm}$ were found to be significant predictors of recurrence. A 3-year DFS rate of 89%, 73%, and 43% for stages IB-IIA, IIB and III, respectively, was also reported. Of note, among the operated patients these rates increased to 100%, 81% and 66% for stages IB-IIA, IIB and III, respectively [96].

Hemoglobin levels have also been suggested to correlate with response to neoadjuvant chemotherapy: In a relevant study [99] that evaluated 73 patients with cervical cancer stage IB2-IIB who received platinum-based neoadjuvant chemotherapy followed by radical hysterectomy, multivariate analysis projected hemoglobin levels as the most powerful prognosticator of response to neoadjuvant treatment. In particular, patients with a pretreatment hemoglobin level $\geq 12\text{mg/dl}$ had significantly longer survival compared to patients with a lower hemoglobin level at diagnosis ($p = 0.008$) [97]. In addition to laboratory measurements, the importance of pathological response characteristics was emphasized in a study that evaluated four different cohorts of patients with locally advanced cervical carcinoma (stages IB2-IIIb) who were included in prospective phase II protocols of neoadjuvant chemotherapy with: 1) cisplatin and gemcitabine, 2) oxaliplatin and gemcitabine, 3) carboplatin and paclitaxel and 4) chemo-radiation with cisplatin or cisplatin and gemcitabine followed in all cases by radical hysterectomy [100]. One hundred and fifty three patients treated within these trials were analyzed to show that pathological response was the only factor predicting relapse, since only 6.6% of patients with pathological complete response (pCR) as compared with 26.8% of patients with viable tumor, relapsed ($p = 0.001$). OS rate was 98.3% in patients achieving a pCR versus 83% for patients with remnant viable

tumor ($p = 0.009$) [98]. A smaller French study suggested as important predictive factors of decreased sensitivity to neoadjuvant chemo-radiotherapy the menopausal status, parametrial invasion, lymphovascular space invasion and mucinous histological subtype [99]. Finally, as platinum-based neoadjuvant chemotherapy is widely administered in that setting, the enzyme excision repair cross complement 1 (ERCC1) immunohistochemical negativity was recognized as an independent predictor for responsiveness to neoadjuvant platinum-based chemotherapy ($p = 0.021$) [100].

The identification of patients with persistent nodal involvement after chemotherapy is crucial for patient prognosis in the neoadjuvant setting [101]. The use of computed tomography (CT) scan or magnetic resonance imaging (MRI) demonstrates a relative sensitivity in the detection of locoregional lymph node involvement. Positron emission tomography (PET) scan seems to have superior sensitivity, especially in the detection of paraaortic lymph nodes [102]. The false-negative rate and negative predictive values of PET-CT imaging for pelvic nodal involvement were 13% and 87%, respectively, in another study that evaluated the histological results of pelvic lymphadenectomy in 16 patients treated for early-stage cervical cancer who had no nodal uptake on ^{18}F -fluorodeoxyglucose (FDG) PET [103]. The prognostic significance of the maximum standardized uptake value [SUV(max)] of FDG as measured by PET was assessed in pelvic lymph nodes of 83 patients with stages IB1 to IIIB cervical cancer: The SUV(max) for the most FDG-avid pelvic lymph nodes was found to be correlated with an increased risk of persistent disease after treatment ($p = 0.0025$), specifically within the pelvic lymph node region ($p = 0.0003$) and also to be predictive of an increased risk of ever developing pelvic disease recurrence ($p = 0.0035$) [106]. Patients with a higher SUV(max) for the most FDG-avid pelvic lymph node were found to have significantly worse disease-specific ($p = 0.023$) and OS ($p = 0.038$). The authors concluded that SUV(max) for the most FDG-avid pelvic lymph node may be used as a prognostic biomarker, able to predict treatment response, pelvic recurrence risk, and disease-specific survival in patients with cervical cancer [104]. The same group of investigators demonstrated that nodal involvement detected by FDG-PET in cervical cancer relates to clinical stage, is comparable to historical data, and stratifies patient recurrence and survival outcomes. Of note, the hazard for disease recurrence increases incrementally based on the most distant level of nodal disease: Pelvic 2.40 (95% CI, 1.63 to 3.52), para-aortic 5.88 (95% CI, 3.80 to 9.09), and supraclavicular 30.27 (95% CI 16.56 to 55.34) [105]. Finally, Doppler vascularity index has been examined as a prognostic index to neoadjuvant chemotherapy in cervical cancer [106].

On the other hand, surgical laparotomy staging (compared with radiographic exclusion) of positive paraaortic lymph nodes in patients with cervical cancer who received chemo-radiation has been validated in a trial [109] that re-evaluated 555 patients who participated in one of the following three phase III GOG trials: GOG 85, GOG 120 and GOG 165. Patients

who had negative lymph node status as determined by surgical sampling (mandatory in GOG 85 and GOG 120 and optional in GOG 165) were compared to patients who had negative lymph node status determined exclusively radiographically (GOG 165). In multivariate analysis, the radiographically determined group was independently associated with a poorer prognosis compared with the surgical sampling group (for disease progression: HR=1.35, 95% CI, 1.01-1.81; for death: HR=1.46, 95% CI 1.08-1.99) [107].

Of note, the timing and dose intensity of cisplatin-based neoadjuvant chemotherapy appeared to have an important impact on whether or not it benefits women with locally advanced cervical cancer according to a systematic review and individual patient data meta-analysis [108] designed to assess the effect of neoadjuvant chemotherapy in two settings. In the first one, neoadjuvant chemotherapy followed by radical radiotherapy was compared with radiotherapy alone, using individual data from 18 trials including 2,074 patients. A marginal survival benefit was suggested only in trials using intensive chemotherapy regimens (cycle lengths of 14 days or shorter). In the second setting, neoadjuvant chemotherapy followed by surgery was compared with radical radiotherapy alone, combining individual data from 5 trials including 872 patients. The results indicated a significant reduction in the risk of death with neoadjuvant chemotherapy (HR=0.65, 95% CI=0.53-0.80, $p=0.0004$), but there were some inequalities between the trials with respect to their design and reporting of the results.

TOXICITY CONSIDERATIONS

Improvements in efficacy have been accomplished by the adoption of multiple and more intensive chemotherapy regimens, yet the median duration of remission in these studies is up to 4-5 months, and they are associated with significant grade 3/4 toxicities. Toxicity is a major concern for women with cervical cancer who are often elderly with poor performance status and considerable co-morbidities. Prior radiotherapy is common in this population and may compromise bone marrow reserves and also renal function through obstruction of ureters. Drug-related toxicities are arguably even more significant in the palliative setting.

Patients with cervical cancer are often not suitable candidates for cisplatin chemotherapy. Peripheral neuropathy is usually not significant as the majority of combinations use doses of cisplatin up to 50mg/m². Carboplatin-related myelosuppression is a major concern in previously irradiated patients. Overall, the use of various chemotherapeutic combinations with different toxicity profiles is associated with a broad spectrum of adverse events in a group of patients that is already frail, bears substantial co-morbidities and is usually elderly. Intensification of chemotherapy with the use of platinum-based triplets and combined administration of agents that share common toxicities (e.g., peripheral neurotoxicity by both cisplatin and paclitaxel) further complicate the situation. The incorporation of molecular targeted agents in

modern therapeutic schedules, despite the theoretical "selective" targeting of these agents, has added a whole new spectrum of treatment-related toxicities, including skin reactions, thrombosis, metabolic disorders, hypertension and diarrhea, which, in their severe forms, can be quite debilitating. For these reasons, therapeutic strategy should be individualized and adapted to the specific morbidity profile of each patient. Efforts should be made to combine chemotherapeutic agents that do not share common toxicities and do not oppose the medical history of the patient.

PROGNOSTIC AND PREDICTIVE MARKERS IN ADVANCED CERVICAL CANCER

Although several prognostic models that include age, serum squamous cell carcinoma (SCC) antigen, tumor size, hydronephrosis, pelvic structures invasion and lymph node metastasis were developed for predicting overall survival in the locally advanced setting of cervical cancer, in metastatic disease efforts are directed at biological cell-markers and markers involved in EGFR signaling and angiogenesis. Implication of such markers in prognosis could also facilitate modern therapeutic research.

In the only analysis of three phase III GOG studies of cisplatin monotherapy versus combinations [109], that evaluated prognostic factors for predictive modeling among 428 patients, multivariate analysis identified age, African-American race, ECOG PS more than zero, pelvic disease, use of prior radiosensitizer and recurrence interval less than 1 year as independent prognostic factors for poor response (all parameters) and increased risk of death (except for age and race). When patients were classified according to those variables, those with 4-5 risk factors were estimated to have a response rate of only 13% and a median progression free and overall survival of 2.8 months and 5.5 months respectively. The authors concluded that the latter group should be considered for non-cisplatin chemotherapy or investigational trials [109]. Diagnosis at age of at least 65 years has been correlated with suboptimal cervical cancer screening pattern and poor survival in a retrospective analysis of cervical cancer patients [110]. In another study that recruited 44 patients with advanced cervical cancer and 10 controls in order to determine the prognostic value of various biologic markers of tumor angiogenesis, univariate analysis demonstrated that tumor response was predicted by the tumor size, the expression of mRNA VEGFR2 levels and the patient's age [111]. Additionally, from *in vitro* models, high Bmi-1 expression in cervical cancer was significantly correlated with poor tumor differentiation, advanced stage, positive lymph node metastasis and shorter survival, identifying thus high Bmi-1 expression in both univariate and multivariate analysis as an independent prognostic factor [112]. From a recent systematic review of the prognostic and predictive significance of cell biological markers in advanced disease that comprised 42 relevant studies, cyclooxygenase-2, serum SCC antigen levels and markers involved in EGFR

signaling (EGFR and HER2), angiogenesis and hypoxia (carbonic anhydrase 9 and hypoxia inducible factor 1a) were also associated with poor prognosis [113]. Finally, pretreatment levels of antioxidant-oxidant parameters such as lipid peroxide [114] and type-1 cytokines (IL-1, IFN γ) [115] and the extent of their change during treatment have been attributed a predictive significance as far as the therapeutic response to neoadjuvant chemo-radiation is concerned. Nevertheless, apart from the well established clinicopathological parameters mentioned above, no biological marker has been able to reliably and reproducibly predict response to treatment and, therefore, no such marker has been implemented in clinical practice to date.

FUTURE DIRECTIONS

Over the past four decades, systemic treatment of advanced cervical cancer has evolved from cisplatin monotherapy to sophisticated combination regimens of platinum-based or non-platinum-based doublets and triplets that may also incorporate biological agents. It seems that cisplatin-based doublets have reached a therapeutic plateau in terms of efficacy and effect on progression-free and overall survival. Therefore, the need for more effective doublet or even triplet combinations implementing molecular targeted agents in an effort to increase anti-tumor activity, while maintaining toxicity

in acceptable levels, is expected to drive scientific efforts in the future. Accumulating data from preclinical studies is increasingly providing clinicians with potent therapeutic targets that are already being evaluated in early-phase clinical trials. Moreover, high throughput whole genome analysis has been recently implemented in the field of cervical cancer research in an effort to identify either genes associated with propensity for metastasis and disease progression [116], or microRNA (miRNA)-based signatures for the prediction of cervical cancer survival [117]. A critical field of intensive research will also be the identification of robust predictive makers for tumor response to chemotherapy or biological therapy that could reliably guide the clinician to select the most appropriate treatment for each individual subject. Such an approach, which is currently hindered by the lack of potent biomarkers, would enable the delivery of the optimal, i.e. the most active therapeutic regimen, and at the same time, obviate unnecessary toxicity from inactive drugs in the specific setting. A number of studies of translational research are addressing these issues and answers to these questions are highly anticipated in the near future.

Conflict of interest statement

The authors declare no conflict of interest.

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Recent developments in non-Hodgkin lymphoma (NHL) treatment

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ABSTRACT

The use of therapeutic monoclonal antibodies in the treatment of malignant diseases has evolved into a promising approach over the past decade. The treatment of non-Hodgkin lymphoma has changed dramatically since the introduction of rituximab, a monoclonal antibody that binds to the B-cell transmembrane protein CD20 and causes lysis of the lymphoma cells. Since then, a number of additional antibodies have been tested against other B-cell targets, resulting in variable efficacies. The goal of these newer agents is to achieve similar or better response rates as seen with rituximab and perhaps demonstrate activity in rituximab-refractory disease. The success of anti-CD20 therapy in B-cell lymphoma is prompting investigators to search for a similarly efficacious monoclonal antibody in T-cell lymphoma and clinical trials with a new anti-CD30 agent are hopeful in anaplastic CD30 positive T-NHL. Among new agents, proteasome inhibitors and immunomodulatory drugs seem to play a pivotal role in the regulation of several cell pathways involved in the development of lymphomas and the antitumor activity of these agents may improve complete remission rates with less toxic regimens.

Key words: lymphoma; treatment; immunotherapy; radioimmunotherapy; monoclonal antibodies; anti-CD20; rituximab.

Abbreviations

NHL, non-Hodgkin lymphoma; PTCL, peripheral T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; MCL, mantle cell lymphoma; DLCL, diffuse large-cell lymphoma; mAb, monoclonal antibody; RIT, radioimmunotherapy; HDACs, inhibitors of histone deacetylases; IMiDs, immunomodulatory drugs; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CR, complete response; OS, overall survival; PFS, progression-free survival; FDA, Food and Drug Administration; SEER, Surveillance Epidemiology and End Results.

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are malignant diseases originating from clonal transformation of B- or T-cells, at various stages of maturation. The traditional implementation of empiric combination chemotherapy, the golden-standard treatment approach for NHLs for decades, designated NHLs

among the most chemotherapy-responsive human malignancies. The recent introduction of new biological modalities, such as monoclonal antibodies, revolutionized treatment policies and improved clinical outcomes, mainly complete response (CR) rates. However, NHLs continue to rank as a prominent cause of cancer-related mortality, as in certain clinical and biological settings the improvement of overall survival (OS) rates was disappointingly modest [1, 2].

The complexity of NHL therapeutics is mainly ascribed to the disease's pronounced heterogeneity, be that clinical or histological, as well as biological or molecular. The unprecedented success of the anti-CD20 monoclonal antibody (mAb) Rituximab in the treatment of NHLs ushered in an increasing exploration of therapies focusing on the biological characteristics of the lymphomatous clone and clone-host interactions. Reviewing recent available data, this article discusses the current status of targeted therapeutic approaches in NHLs concerning monoclonal antibodies and provides some comments that may be of use for the practicing clinician.

TARGETED MONOCLONAL ANTIBODIES

Major advances in antibody-mediated immunotherapy emerged in 1975 when mAb production was substantially developed, making it feasible to produce large quantities of antibodies directed against specific antigenic cellular targets. The first cancer therapeutic Abs of animal origin were subsequently replaced by hybrids composed of primate antibody regions linked with a human backbone. Being potent inducers of human effector functions, such as antibody-dependent cellular toxicity (ADCC) and complement dependent cytotoxicity (CDC) these genetically engineered Abs, referred to as chimeric or humanized, showed enhanced anti-tumor efficacy as well as a significantly lower incidence of adverse immune reaction compared to cross-species Abs. In 1997, the FDA approved the first anti-CD20 mAb, Rituximab (MabThera®), for the treatment of relapsed CD20+ B-cell NHL. Since then, several mAbs targeting surface antigens and receptors have been developed and tested, both clinically and pre-clinically, with varying success, whilst three naked (Rituximab, Ofatumumab and Alemtuzumab) and two radioimmune mAbs (⁹⁰Ibritumomab tiuxetan and ¹³¹I-Tositumomab) have been approved by the FDA for the treatment of B-cell lymphoid malignancies [1, 2].

B-cell lineage-specific antigens

The pan-B-cell marker CD20 constitutes an ideal target for mAb anti-lymphoma therapy as it is exclusively expressed on benign and malignant B-cells, with minor modulation during B-cell differentiation and insignificant secretion in circulation. The cytotoxic activity of mAbs directed against CD20 positive cells is thought to be based on ADCC activity via natural killer responses, or CDC which results in the formation of the membrane attack complex and subsequent cell lysis, or by the induction of cell signaling followed by apoptosis.

The first-generation anti-CD20 recombinant humanized mAb Rituximab is an IgG1 chimeric antibody containing murine light- and heavy-chain variable region sequences and human constant region sequences [3]. Rituximab made a large impact on treatment of both indolent and diffuse B-cell NHLs. Recent data from the Surveillance Epidemiology and End Results (SEER) database and retrospective analysis of clinical trials in indolent NHL suggest an improved OS with the use of Rituximab, although 50% of patients with relapsed or refractory follicular NHL do not respond to initial therapy with Rituximab and close to 60% of patients who were previously treated with Rituximab no longer benefit from retreatment. A series of phase II and III studies have assessed the efficacy and safety of Rituximab monotherapy in relapsed/refractory indolent NHL. Objective responses ranged between 21% and 63%, with only a minority showing CR [4]. When compared to studies using Rituximab as monotherapy, combination schemes with Rituximab and chemotherapy in pretreated patients with follicular NHL was associated with improved OR and CR rates; yet most patients were not cured, experiencing relapses after a median of 4 years [5, 6]. By virtue of its low

toxicity profile, the possible benefits of various schemes of Rituximab maintenance were investigated. A recent meta-analysis of follicular NHL trials comparing Rituximab maintenance with no maintenance showed that patients with refractory or relapsed disease treated with Rituximab maintenance had improved OS, whereas previously untreated patients had not survival benefit. This meta-analysis further supported the use of Rituximab maintenance in the standard of care for relapsed or refractory follicular NHL [7].

Taking into consideration the fact that toxicity profiles of chemotherapy and Rituximab do not overlap and Rituximab is able to sensitize lymphoma cells to chemotherapy, a variety of chemo-immunotherapy combinations have been used in the primary treatment of low-grade lymphomas at advanced stage and high-grade lymphomas. Several randomized, phase III trials of patients with advanced stage indolent lymphoma showed improved CR and EFS rates in patients treated with Rituximab combined with various chemotherapeutic schemes. Although numerous data underline that the concept of concurrent Rituximab-chemotherapy application should be followed in order to achieve the ultimate treatment outcome, there is not explicit information yet to answer the crucial question of whether combined immune-chemotherapy also prolongs the OS of patients with advanced indolent lymphoma.

Over the past few years, new generations of anti-CD20 mAbs have been developed aiming at biological and clinical superiority over Rituximab. Second generation mAbs, Ofatumumab (Arzerra®), Veltuzumab and Ocrelizumab, are humanized or fully human, but with an unmodified Fc region. Ofatumumab targets a different small-loop epitope of CD20 compared with Rituximab; its close binding proximity to the B-cell membrane results in highly efficient complement membrane-deposition, with minimum systemic release of activated complement components. Recent laboratory studies confirmed that Ofatumumab is more effective than Rituximab in inducing CDC and cell killing. Ofatumumab monotherapy of heavily pretreated or chemotherapy refractory follicular NHL patients resulted in a 10% overall response rates (ORR), with stable disease being observed in 50% of treated patients. Of note, 22% ORR was recorded in patients who were refractory to prior Rituximab monotherapy [8, 9, 10, 11].

CD52 is a glycosylphosphatidylinositol anchored low molecular weight glycoprotein expressed on the surface of B and T lymphocytes, natural killer (NK) cells, monocytes, macrophages, and some dendritic cells. Alemtuzumab (Campath®) is a humanized monoclonal antibody that recognizes the CD52 antigen. It has demonstrated significant activity against a number of B-cell malignancies, particularly in refractory and relapsed chronic lymphocytic leukemia and, in addition, it shows interesting activity in T-cell lymphomas [12, 13]. Alemtuzumab has been incorporated in first-line chemotherapy treatment protocols [6, 14], however the association with increased risk of opportunistic infections makes it unattractive in clinical settings [12-14].

The clinical success of Rituximab expanded research of other potential targets in the area of mAbs, including CD22, CD19 and CD80 antigens. Epratuzumab, Blinatumomab and Galiximab are the perspective mAbs to the previous targets and preliminary results about their efficacy and toxicity profile are available [1].

Radioimmunotherapy (RIT) is a safe, effective and significantly underutilized therapy for patients with B-NHL. Multiple studies have demonstrated the efficacy of ^{90}Y -Ibritumomab tiuxetan and ^{131}I -tositumomab in the setting of relapsed/refractory indolent B-NHL. However, to date no comparative study has shown an advantage in OS. ^{90}Y -Ibritumomab (Zevalin®) has been approved for the frontline treatment of follicular B-NHL in patients responding to induction chemotherapy and several trials are performed using ^{90}Y -Ibritumomab in patients with high-grade NHL as a consolidation treatment or added to reduced-intensity allogeneic stem-cell transplantation regimens. ^{131}I -tositumomab (Bexxar®) has been approved for patients with follicular B-NHL, with or without transformation, with disease refractory to Rituximab, relapsing following chemotherapy [15, 16]. RIT with ^{131}I -Rituximab is much more effective than Rituximab alone, and the overall response rate is at least as good as that of Rituximab-chemotherapy regimens, without the associated toxicity [17].

T-cell lineage-specific antigens

T-cell neoplasms, such as adult T-cell leukemia/lymphoma (ATL) and peripheral T-cell lymphoma, are particularly aggressive and, despite novel combination chemotherapy regimens, still have extremely poor prognoses. There is an unmet medical need for novel therapies and the anti-chemokine CCR4 receptor antibody Mogamulizumab (Poteligeo®) may offer such an option for the treatment of ATL. Mogamulizumab is a humanized antibody, with a defucosylated Fc region, which enhances antibody-dependent cellular cytotoxicity. As a result, Mogamulizumab demonstrates potent antitumor activity at much lower doses than other therapeutic monoclonal antibodies [18].

The antigen CD30 is overexpressed in Hodgkin lymphomas and some NHLs like anaplastic large-cell lymphomas and adult T-cell lymphomas, which makes it a suitable target for antibody-based therapies. Brentuximab vedotin (Adcetris®) is a chimeric anti-CD30 antibody conjugated via a protease-cleavable linker to the potent anti-microtubule agent monomethyl auristatin E (MMAE). Following binding to CD30, brentuximab vedotin is rapidly internalized and transported to lysosomes where MMAE is released and binds to tubulin, leading to cell cycle arrest and apoptosis [19]. In anaplastic large-cell lymphoma, a phase II trial with 58 patients led to an ORR of 86% with a median duration of 12.6 months [20].

Other targets such as CD45 antibodies are under investigation and preliminary results show *in vitro* and *in vivo* lytic activity against primary cells and cell lines derived from NK

and T-NHLs. Hematopoietic toxicity seems to be the most important adverse event which could be used as an adjunct to the conditioning regimen for allogeneic stem cell transplantation in CD-45 positive NK and T-NHLs [21].

IMMUNOMODULATORY DRUGS

Lenalidomide (Revlimid®) is a thalidomide analogue with anti-angiogenic, anti-tumorigenic, and immunomodulating activity. The mechanism of action that mediates the immunomodulatory function is poorly understood; the design of effective therapeutic combinations with Lenalidomide is dependent on our understanding of the immunomodulatory potentials of the drug, its microenvironmental interactions within lymphomatogenous niches as well as its specific bioactivity [22].

Recently, Lenalidomide has been studied in patients with various histological subtypes of B-NHLs, both in low and high grades. Multiple trials that enrolled patients who had failed more than two prior systemic therapies and received salvage treatment with Lenalidomide monotherapy, resulted to ORR 35%, with 13% CR. Noticeably, responses were also observed in aggressive histological subtypes, with MCL and advanced-grade follicular types showing responses of about 42%, with an estimated median response duration of 6.2 months [23].

INHIBITORS OF SPECIFIC MOLECULAR PATHWAYS

Suppression of proteasome function with the first-in-class small molecule inhibitor Bortezomib (Velcade®) is a rational therapeutic strategy against several hematological malignancies, including NHLs and may enhance the activity of chemo-immunotherapy [24]. Assessment of patients with DLBCL and MCL treated with R-CHOP plus bortezomib showed ORR 100% with 86% CR, 2-year OS of 70% and ORR was 91% with 72% CR, and 2-year OS 86% respectively [25].

Targeting the mTOR pathway offers a new approach to anti-lymphoma treatment. mTOR inhibitors have been developed and used in MCL and clinical trials in other high-grade lymphomas are as well ongoing. Temsirolimus (Torisel®) has been approved in treating relapsed or refractory MCL with ORR 38% in a phase II clinical trial [26].

Another promising approach towards drugs that modulate epigenetic processes has been seen in the development of inhibitors of histone deacetylases (HDACs) which regulate histone acetylation in nucleosomes. Vorinostat (Zolinza®) and Romidepsin (Istodax®) have been approved for treating cutaneous T-cell lymphoma (CTCL) with progressive, persistent or recurrent disease and are shown to reach response rates at 30% [27].

DISCUSSION

New therapies alone and in combination with old therapies have demonstrated an improvement in NHL outcomes.

Nevertheless, new treatment modalities with improved toxicity profile and even better responses are needed. Although Rituximab has revolutionized the treatment of NHLs, still many patients relapse or remain refractory. This has initiated intense research to develop more potent anti-CD20 antibodies.

Clinical advantages of second generation anti-CD20 mAbs and of other lymphoma targets should be proven by well-designed clinical trials in Rituximab-refractory patients. Even though CD20 expression is an eminent feature of specific B-NHLs, many patients fail to respond or become resistant to anti-CD20 mAbs, indicating that beyond CD20 expression other biological, host or lymphoma factors modulate responsiveness. Nevertheless, the fact that third-generation mAbs, such as PRO131921, AME-133v and GA-101, are currently being developed proves that CD20 remains unchallenged as a mAb target in NHL therapeutics [1, 2, 10].

Except for monotherapy with mAbs or combined immunotherapy-chemotherapy, RIT with anti-CD20 mAbs demonstrated excellent clinical efficacy in B-NHL, mostly follicular NHL. However, due to the complexity of delivery compared with naked antibodies, and concerns about late toxicities, it is

difficult for the clinical community to integrate it in standard chemotherapy regimens [12-14].

Antibodies targeting antigens other than CD20 have shown less encouraging clinical efficacy. However, other new-generation antigens are under clinical investigation demonstrating substantial clinical efficacy in phase I/II trials and arousing hopes for an improved outcome in Rituximab-refractory NHL.

Targeting molecular pathways is another promising treatment option and new drugs have essentially been evaluated in patients with recurrent disease or refractory to first-line regimens. Among new agents, bortezomib seems to play a pivotal role in the regulation of several cell pathways involved in the development of lymphomas and HDAC inhibitors will likely be incorporated into combinations of targeted therapies, both in the upfront and relapsed disease setting. The molecular basis of their antitumor activity is an area of vigorous study, which will hopefully lead to further improvements in the near future.

Conflict of interest statement

The authors declare no conflict of interest.

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Metastatic renal cell cancer: what is the sequential treatment for long-term clinical benefit?

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ABSTRACT

Renal cell carcinoma (RCC) accounts for 2-3% of all adult malignancies. Metastatic RCC (mRCC) has a poor prognosis and is largely resistant to chemotherapy. Until recently, systemic treatment was limited to cytokine therapy, associated with low rates of response and high rates of toxicity. In the past 6 years, treatment options have expanded with specific molecular-targeted therapies directed at the VEGF and the mTOR signaling pathways. On this basis, sequential treatment with targeted agents has become the actual standard of care. However, the optimum sequencing approach to maximize long-term clinical benefit remains still under investigation. In the first-line setting, treatment with a VEGFr-TKI is recommended for most patients. ESMO guidelines indicate sunitinib, bevacizumab + INF- α and pazopanib as the most efficacious treatments for favourable/intermediate-risk patients, whereas temsirolimus is recommended for poor-risk patients. However, most mRCC patients eventually develop resistance to these agents. At that stage, clinicians face the important question of which is the optimum treatment sequencing to overcome resistance to first-line agents. According to ESMO guidelines, both the mTOR inhibitor everolimus and the VEGFR inhibitor axitinib are recommended second-line treatment options following VEGFR inhibitors. However, there is no evidence that a change in mechanism of action following anti-angiogenic targeted agents would result in better outcomes compared with maintaining VEGFR inhibition in the second-line setting. Available data support both TKI to TKI and TKI to mTOR sequencing. Until data from ongoing trials are available, clinicians should take into account patient, disease characteristics and drug toxicity profile to make treatment decisions.

Key words: renal cell cancer; anti-angiogenic agents; mTOR inhibitors; sequential treatment.

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 2-3% of all adult malignancies, representing the seventh most common cancer in men and the ninth most common cancer in women [1]. RCC is diagnosed in about 170,000 people worldwide annually, resulting in 72,000 deaths [2]. Many patients present with advanced or unresectable disease, and up to 30% of patients who have initially localized disease will eventually relapse [3]. Metastatic RCC (mRCC) has a poor prognosis, with an estimated 5-year relative survival of 11% among those with distant metastases in the USA over the period 2001 to 2007 [4].

Until recently, systemic treatment was limited to cytokine therapy with *either* interleukin (IL)-2 *or* interferon (INF)- α , because mRCC is largely resistant to chemotherapy [5]. Cytokine treatment was based on the rationale that immune system stimulation kills cancer

cells. However, in patients with mRCC, cytokine therapy is associated with low rates of response and high rates of toxicity in the first-line setting [5]. In the second-line setting (in patients who have progressed on one cytokine), even fewer responses are observed while toxicity remains similar to that of first-line use [6]. Consequently, new therapies were needed to improve outcomes in patients with mRCC.

RCC is a highly vascularized tumor, in which pro-angiogenic mechanisms are mostly triggered through the inactivation of the von Hippel Lindau (VHL) gene [1]. The VHL gene is inactivated in >75% of the cases of clear cell RCC, either by deletion or promoter methylation. This leads to a defective VHL protein and activation of hypoxia inducible factors (HIFs), which translocate to the nucleus and activate transcription of many pro-angiogenic factors, including vascular endothelial growth

factor (VEGF), platelet-derived growth factor (PDGF) and transforming growth factor alpha (TGF- α). VEGF has a dominant role in the angiogenic process; binding of VEGF to VEGFR2 activates upregulation of molecules involved in mediating proliferation, migration and survival of endothelial cells and promoting vascular permeability. Therefore, inhibition of angiogenesis represents a principal target of mRCC therapy.

Mammalian target of rapamycin (mTOR) is a serine/threonine kinase that plays a critical role in regulating cellular processes that control growth, proliferation, motility and angiogenesis [7]. mTOR is regulated by both the phosphoinositol-3-kinase (PI-3K)/Akt pathway and the mitogen-activated protein kinase (MAPK) pathway. The mTOR complexes have a critical role in orchestrating changes in cell growth and metabolism in response to a wide variety of inputs including nutrient availability, growth factor levels, cellular energy alterations and stress.

As information regarding aberrant activities of signal transduction pathways in RCC became available, specific molecular-targeted therapies were identified, directed at the VEGF and the mammalian target of rapamycin (mTOR) signaling pathways, as both VEGF and mTOR activities were shown to be involved in the pathogenesis of mRCC [8].

In the past 6 years, treatment options have expanded considerably for patients with mRCC, with the approval of seven new molecules for use in the 1st and 2nd-line setting since 2006. These molecules, targeting either the VEGF or the mTOR pathway, have been evaluated in several randomized phase III clinical trials and have significantly improved progression-free survival (PFS) as well as overall survival (OS) for patients with mRCC compared with placebo or with the previous standard of care, immunotherapy [9-16]. On this basis, many patients with mRCC will be candidates for multiple lines of treatment. However, the optimum sequencing approach in order to expose patients to as many agents as possible and maximize long-term clinical benefit still remains under investigation.

FIRST-LINE TREATMENT

A wealth of randomized clinical trials investigating the efficacy of targeted agents in the last few years has provided the basis for the creation of first-line treatment algorithms [10-13, 15]. Recommendations mainly relate to clear cell histology, since most of the pivotal trials have been carried out in this common histological subtype. Guidelines from the European Society of Medical Oncology (ESMO) indicate sunitinib, bevacizumab + IFN- α and pazopanib as the most efficacious treatments for favorable/intermediate-risk patients, whereas temsirolimus is recommended as the current standard of care for poor-risk patients [17] (Figure 1).

New options such as tivozanib (presented at ASCO 2012 by Motzer *et al.*) might become available for 1st-line treatment in the near future. It is clear that for many bad prognosis

patients, best supportive care remains the only suitable treatment option. In addition, since some mRCC patients have a very indolent disease course a period of observation before starting treatment should be considered.

A number of new studies add information on the efficacy and toxicity of targeted agents. The double-blind PISCES study evaluated patient preference based on toxicity profile of two different sequences of treatment: pazopanib given for 10 weeks and then after a 2-week washout, sunitinib for 10 more weeks, or the reverse sequence. Both drugs were given at the standard doses and schedules, 800mg once daily for pazopanib and for sunitinib, 50mg once daily (4 weeks on treatment, followed by 2 weeks off treatment and then 4 weeks on treatment) [18]. 70% of the patients preferred pazopanib versus 22% sunitinib due to better quality of life and less fatigue. The number of patients who were not able to express a preference was less than 10%. This study design does not allow an efficacy comparison, but clearly demonstrated the better tolerability of pazopanib over sunitinib [18].

A comparison between the two drugs has just been reported with the presentation of the results of the COMPARZ study, a non-inferiority trial of pazopanib versus sunitinib in previously untreated mRCC patients [19]. Using the same dosing and schedule as the PISCES trial, the COMPARZ trial demonstrated that pazopanib is not inferior to sunitinib in terms of progression-free survival (PFS was 8.4 months for pazopanib versus 9.5 months for sunitinib).

Given the growing number of available first-line targeted agents, treatment decision should be based both on efficacy data and clinical experience.

Prognostic models that combine multiple clinical factors are often used in clinical management. The most widely used model is the one developed by the Memorial Sloan-Kettering Cancer Center (MSKCC), using a database of 400 patients who received interferon-based therapy [20]. This model stratified prognosis as favorable, intermediate, or poor, based on lactate dehydrogenase levels, performance status, serum calcium concentrations, hemoglobin levels and time from diagnosis to treatment. Median overall survival in the favorable-prognosis, intermediate-prognosis and poor-prognosis groups was 30 months, 14 months and 5 months, respectively [20]. As the model was developed using patients treated with interferon-based regimens, the MSKCC model is useful for identifying patients who may benefit from immunotherapy.

The MSKCC model has also been validated and updated for use in the current era of targeted therapies as the Heng criteria, including four of the five prognostic components of the MSKCC model with the addition of platelet and neutrophil counts as further prognostic indicators. In 2009, Heng *et al.* [21] conducted a large multicenter study of 645 patients to better define the prognostic indicators for overall survival in mRCC patients treated with VEGF-targeted therapy (sorafenib, sunitinib and bevacizumab). Patients are stratified into

Figure 1.RCC Treatment Algorithm, Escudier B, *et al.*; Ann Oncol 2012.

RCC Treatment Algorithm: 2012

Treatment Status	Patient Status	Therapy (Level 1 Evidence)	Other Options (≥ Level 2)
First Line	Good or intermediate risk	Sunitinib Bevacizumab + IFN Pazopanib	High-dose IL-2 (Sorafenib) Observation Clinical Trial
	Poor risk	Temsirolimus	Sunitinib Pazopanib Clinical Trial
Second Line	Failed cytokines	Sorafenib Pazopanib Axitinib	Sunitinib Bevacizumab Clinical Trial
	Failed VEGFR inhibitor	Everolimus Axitinib	TKI's Temsirolimus
	Failed mTOR inhibitor	?	Clinical Trial

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favorable, intermediate and poor-prognosis groups according to the presence of six risk factors: performance status, hemoglobin levels, serum calcium concentration, time from diagnosis, neutrophil count and platelet count [21]. Median overall survival in the favorable-prognosis group was not reached at the time of the report; overall survival in the intermediate-prognosis and poor-prognosis groups was 27 months and 8.8 months, respectively. In practice, the two above mentioned prognostic models are the most widely accepted and used in treatment decisions.

Nevertheless, in addition to risk factors and prognostic models, clinicians need to take into account factors that are individual to each patient, in order to individualize treatment and improve clinical outcomes. These factors include patient lifestyle, quality of life, comorbidities, symptoms and expectations of therapy.

RESISTANCE TO TARGETED THERAPIES

Sequential treatment with targeted agents is the actual standard of care for patients with mRCC. First-line treatment with a VEGFr-TKI is recommended for most patients with mRCC; however, development of resistance to these agents is common [22]. None of the existing VEGFr-TKIs completely block all angiogenic signaling pathways [23].

Tumor cells can adapt to this incomplete inhibition of angiogenesis, leading to resistance and disease progression. Tumor adaptation and evasion may occur via multiple mechanisms. For example, reestablishment of angiogenesis can occur via mutation, epigenetic programming, or remodeling

of the stromal microenvironment, leading to renewed tumor growth [22]. The importance of tumor microenvironment has been highlighted in a preclinical study of sunitinib-resistant skin metastases transplanted into nude mice; in the mice the tumors were once again sensitive to sunitinib. Similarly, in xenograft models, sorafenib-resistant tumors reacquired sorafenib sensitivity when reimplanted in untreated mice. This data suggests that a change in tumor microenvironment may "reset" tumor responsiveness to targeted therapies. This could be achieved either by providing a treatment break or by switching to another targeted therapy, both of which are therefore important considerations in determining optimum use of targeted therapies in mRCC [24].

Furthermore, despite the reliance of RCC cells on underlying VHL inactivation and resulting VEGF overexpression, several studies have failed to show a clear association between either VHL status or VEGF levels and clinical response to VEGF-targeting agents, further clouding the biology of response and resistance in this setting. Whether this absence of correlation represents "intrinsic" resistance of some tumors or more rapid "adaptive" or "evasive" resistance than can be assessed by traditional clinical measures, remains to be defined [22]. Nonetheless, the fact that studies with more potent VEGF-pathway inhibitors, such as axitinib, have shown tumor shrinkage in more than 80% of patients, suggests, by contrast with other tumor types where angiogenesis is driven by hypoxia rather than VHL loss, in RCC intrinsic resistance is uncommon. In any case, inhibition of VEGF-driven and/or PDGF-driven angiogenesis can trigger compensatory pro-survival responses that might be

important to understanding treatment resistance [22].

For most mRCC patients, resistance to first-line therapy eventually develops, leading to disease progression. At that stage, clinicians face the very important question of when the right time to start second-line treatment is and which is the optimum treatment sequencing that may help patients to overcome resistance to first-line therapeutic agents.

WHEN TO START SECOND-LINE TREATMENT OR RESPONSE ASSESSMENT

Disease progression includes a wide range of clinical scenarios, and therefore clinicians need to use a combination of pathological data, clinical assessment and patient individual factors to decide whether disease progression has occurred and a second-line treatment is needed.

Recent evidence suggests that, whereas Response Evaluation Criteria In Solid Tumors (RECIST) are valid to compare drugs in clinical trials and identify primary resistance to targeted therapies, they are not sufficient to define disease progression in real-life clinical practice, or to evaluate the efficacy of anti-angiogenic therapies that induce necrosis often without changes in tumor size [25]. On this basis, there is an urgent need for improved imaging techniques to enable better characterization of tumors and a fuller understanding of disease progression, thereby enabling physicians to make the most appropriate treatment decisions for each individual patient. Recently developed alternatives to RECIST include functional imaging techniques and dynamic contrast-enhanced ultrasonography [25].

OPTIMAL SEQUENCING STRATEGIES

TKI to TKI sequencing

According to ESMO guidelines [17], both the mTOR inhibitor everolimus and the VEGFR inhibitor axitinib are recommended second-line treatment options following VEGFR inhibitors (Figure 1).

However, in treatment sequencing, there is no evidence that a change in mechanism of action following anti-angiogenic targeted agents would result in better outcomes compared with maintaining VEGFR inhibition in the second-line setting. Cross-resistance has not been observed with the sequential use of VEGFR inhibitors, probably due to their distinct and overlapping inhibitory profiles. Additionally, since tumor progression on a VEGF-targeted agent is thought to be due to changes in molecular pathways used for maintenance of vascular supply, sequential use of VEGF-targeted therapies that have different targets may inhibit successive escape pathways and delay progression further.

The first experience in the consecutive use of anti-angiogenic agents comes from sequential use of sorafenib and sunitinib [26–41]. Four prospective studies evaluated sorafenib as second-line treatment in sunitinib-refractory patients and reported PFS benefits [26–29]. Similarly, several

retrospective studies have shown benefit of a sequence, either with sorafenib followed by sunitinib or vice versa. Additionally, data (mostly retrospective) suggests that sorafenib followed by sunitinib is associated with improved cumulative PFS outcomes compared with sunitinib followed by sorafenib [30–41]. Results from the ongoing randomized, phase III SWITCH trial (sorafenib followed by sunitinib versus sunitinib followed by sorafenib in treatment-naïve patients with mRCC) will provide additional data.

Level 1 evidence supporting dual TKI sequencing comes from the randomized phase III AXIS trial [16]. Two VEGFR tyrosine kinase inhibitors, axitinib and sorafenib, were directly compared in patients with mRCC following failure of one previous systemic therapy. Generally, axitinib led to a statistically significant increase in the PFS compared with sorafenib. Additionally, the subgroup analysis showed a significant superiority of axitinib over sorafenib in the sunitinib-refractory group (The median PFS was 4.8 months for axitinib versus 3.4 months for sorafenib, $p=0.0107$) (Figure 2).

AXIS is the first head-to-head trial of targeted agents in second-line mRCC and its results support sequencing of TKI to TKI. This data suggests that metastatic renal cell cancer remains sensitive to VEGFR inhibition, even after failure of a previous VEGFR inhibitor, although the clinical benefit of VEGFR inhibition might be reduced with subsequent therapy (reduced median PFS compared to the median PFS of the cytokine-refractory subgroup, with both agents). Additionally, according to this data, VEGFR inhibitors should be considered as individual agents rather than a drug class.

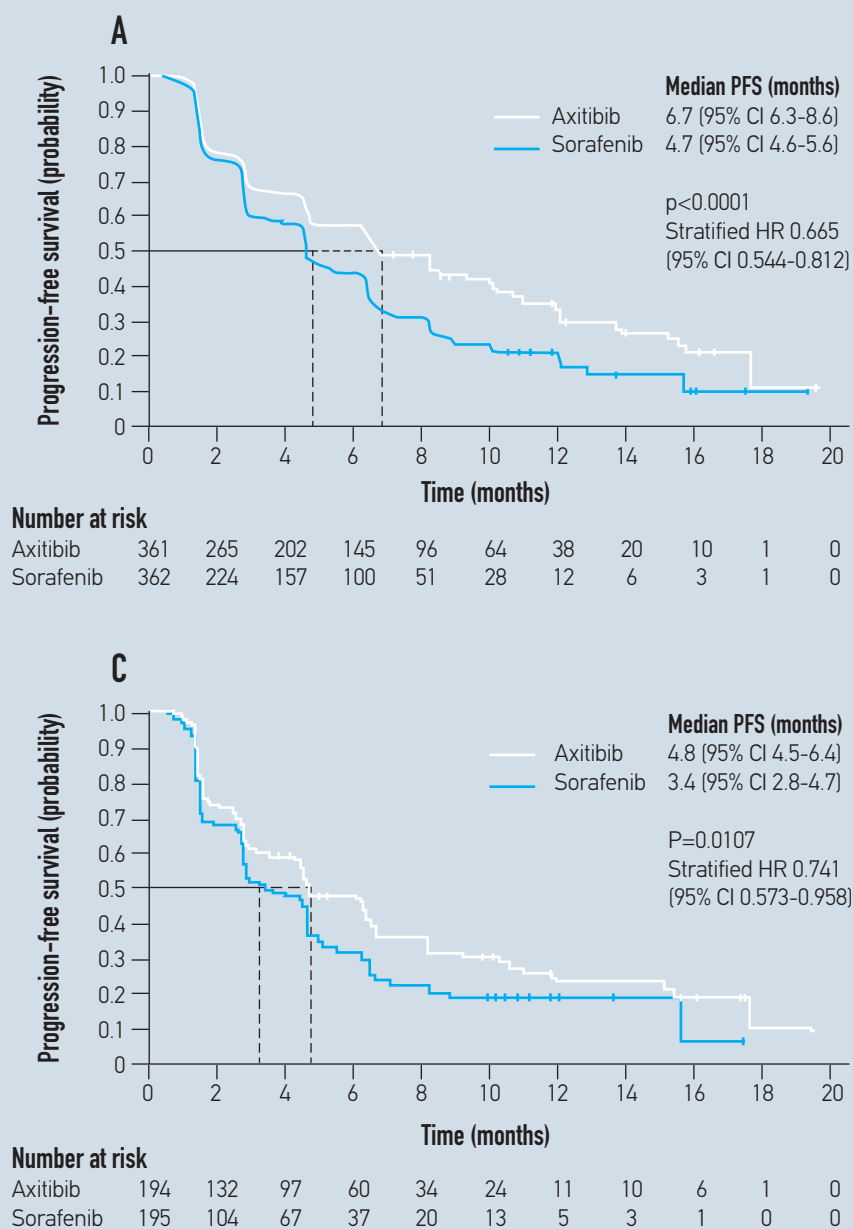
TKI to mTOR sequencing

An alternative to sequencing with VEGF-targeted therapies is to use an mTOR inhibitor. In this setting, RECORD-1 was the first trial demonstrating a PFS benefit in second-line treatment. In this phase III, randomized, placebo-controlled study, everolimus was evaluated in 416 patients with mRCC who had progressed after one to \geq four lines of therapy, including sorafenib and/or sunitinib [14, 42]. Everolimus was associated with a median PFS of 4.9 months in the overall population versus 1.9 months for placebo ($p<0.001$) (Figure 3). In this study, more than three-quarters (79%) of patients had received two or more prior therapies (which, as well as sorafenib/sunitinib could have included bevacizumab, interleukin-2 and/or interferon-alpha) and so received everolimus/placebo as a third-line or later treatment. Only 89 (21%) patients had received one VEGF-targeted therapy. Furthermore, analysis of PFS with everolimus compared with placebo according to prior VEGFR-TKI showed that everolimus was as effective after two VEGFR-TKIs as it was after one and also appeared to be more effective post-sorafenib than post-sunitinib.

Given this data, everolimus may be used in the second-line setting as well as a third-line treatment following two VEGF-targeted agents in sequence. Use of an mTOR inhibitor was

Figure 2.

Kaplan-Meier estimated median PFS in patients who received axitinib or sorafenib as second-line therapy for metastatic renal cell cancer. HR = hazard ratio, PFS = progression-free survival. (A) All patients, (C) patients previously treated with sunitinib based regimen. Rini BI, *et al.*; Lancet 2011.



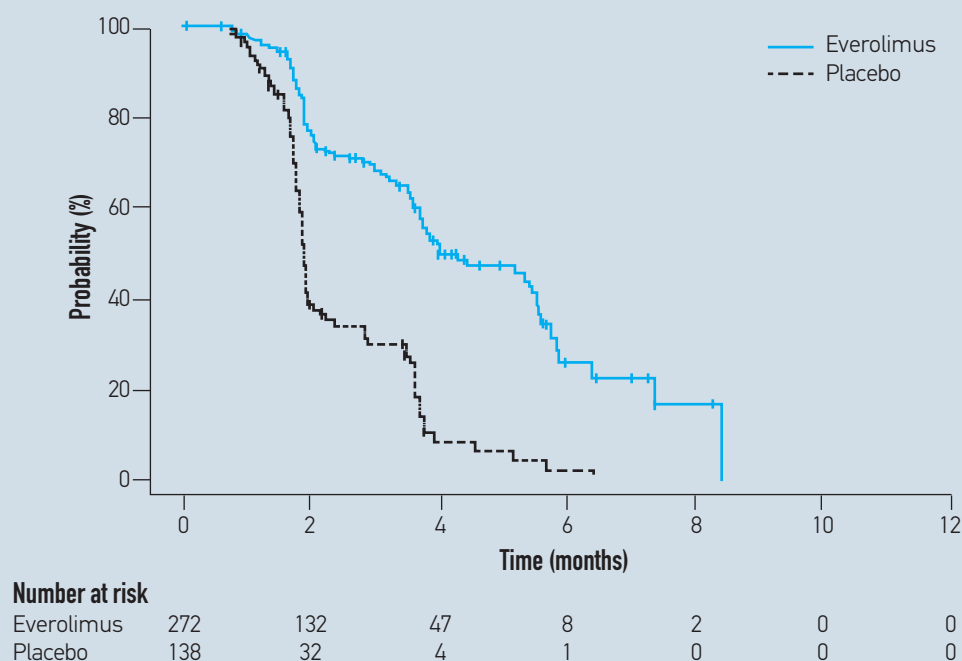
previously expected to be particularly helpful in patients who were refractory to first-line VEGF-targeted therapy, but retrospective data indicates that even those who would seem to be candidates for mTOR inhibitors may benefit from a second VEGF-targeted agent [43]. Further information on the optimal use of everolimus will come from the RECORD-3 trial (NCT00903175), which will assess everolimus followed

by sunitinib versus sunitinib followed by everolimus, and the CALGB90802 study (NCT01198158), which will assess everolimus plus bevacizumab versus everolimus plus placebo following a TKI therapy.

Until recently, available data regarding the use of temsirolimus after VEGFR inhibitors was very limited [44-45]. However, results from the phase III INTORSECT study [46]

Figure 3.

Kaplan-Meier estimates of progression-free survival (PFS). Motzer RJ, *et al.*; Lancet 2008.



evaluating temsirolimus versus sorafenib in patients with advanced RCC whose disease had progressed on or after sunitinib, were presented at the latest 2012 ESMO Congress. Temsirolimus did not meet the primary endpoint of prolonging progression-free survival (PFS) compared to sorafenib. Although PFS was numerically higher in the temsirolimus arm, the difference was not statistically significant (PFS 4.3 months for temsirolimus vs. 3.9 months for sorafenib, $p=0.193$). Overall survival, a secondary endpoint in the study, showed statistical significance favoring patients randomized to the sorafenib arm.

COMBINATION THERAPY

Combination therapy for advanced RCC, involving horizontal or vertical blockade, is currently being investigated with the aim of improving outcomes, although the validity of this approach has not been determined. Horizontal blockade involves inhibition of different molecular pathways involved in the production of cancer-related genes, including VEGF, EGFR and PDGF. This can be achieved using either a combination of specific inhibitors, or multi-targeted agents. Vertical blockade involves targeting the same pathway at two or more levels. For such approaches, it is vital to consider each agent's exact mechanism of action. In particular, a combination of therapies that target different

functional pathways, e.g. cell survival and angiogenesis might have an additive or synergistic effect.

Substantial anti-tumor activity was demonstrated when sorafenib was used in combination with bevacizumab or INF- α , although toxicity was exacerbated [47-48]. Trials involving concomitant administration of sorafenib with other targeted agents are ongoing. Additionally, some studies have investigated combinations involving sunitinib, temsirolimus and/or bevacizumab, with mixed results. However, some combinations have been associated with unacceptable toxicity [49-52]. Currently, the combination therapy approach is not recommended until there is sufficient safety and efficacy data, given the significant increase in the cost of targeted therapies.

BISPHOSPHONATE THERAPY

Bisphosphonate therapy with zoledronic acid has been shown to reduce skeletal related events providing considerable symptomatic benefit in patients with mRCC and bone metastasis, and therefore, it is strongly recommended [53].

Novel agents other than bisphosphonates such as radium-223 and denosumab became recently available for clinical use; however, their precise role in the treatment of bone metastasis from RCC is still unclear.

SURGICAL TREATMENT OF METASTATIC DISEASE

In contrast to the management of other solid tumors, removal of the primary tumor is often performed for patients with mRCC.

Cytoreductive nephrectomy

Nephrectomy is an essential component of vaccine and adoptive immunotherapy protocols [54]. According to the National Comprehensive Cancer Network (NCCN) guidelines, the current standard of care is to consider cytoreductive nephrectomy in all patients who present with potentially surgically resectable mRCC. This standard has been in place for the last decade and is the result of two large randomized trials (the SWOG trial and the European EORTC trial) that evaluated patients randomized to either interferon therapy without surgery or nephrectomy followed by interferon therapy [55–56]. From these two trials, it was clear that there was a survival benefit in patients who received surgery versus those who did not (13.6 vs. 7.8 months, respectively; $p=0.002$).

The optimal integration of surgery with the newer systemic therapies remains a question. The benefits of these targeted therapies have been observed in trials that predominantly enrolled patients after tumor nephrectomy and it remains unclear whether the same results can be achieved in patients without cytoreductive nephrectomy. Systemic treatments with targeted agents could be used upfront and cytoreductive nephrectomy offered to patients who do not progress, but this approach is not proven and could increase surgical morbidity and postoperative complications. Patients who fall into the poor prognosis group according to the MSKCC criteria may not benefit from cytoreductive nephrectomy in the context of systemic treatment with temsirolimus.

Currently, there are several ongoing phase III trials that will shed light on the value of cytoreductive nephrectomy in patients who will receive targeted therapies. For instance, there is an ongoing randomized phase III trial in Europe called CARMENA (NCT00930033), where patients with mRCC and a good performance status (ECOG PS 0 or 1) will be randomized to receive either sunitinib without surgery or nephrectomy followed by sunitinib. Another EORTC trial, SURTIME (NCT01099423), will compare immediate cytoreductive nephrectomy followed by sunitinib with deferred nephrectomy after 3 courses of sunitinib and reintroduction of sunitinib after surgery. Each of these trials will help clarify the utility of nephrectomy in conjunction with targeted therapy in mRCC.

Surgery for metastases

Metastasectomy has never been evaluated in a randomized trial. However, there are clinical situations where it is considered appropriate, including solitary (recurrent) metastasis, limited multiple metastasis, residual mass after response to systemic therapy and palliation [57]. Complete removal of metastatic lesions improves clinical prognosis, with excision of solitary or limited metastases leading to long-term survival (>10 years) in approximately 30% of patients [54, 58]. Metastasectomy should be considered before systemic therapy whenever complete resection of all lesions seems feasible. Patients responding to targeted therapy who are then suitable for metastasectomy may also benefit.

CONCLUSIONS

To date, the improvements in PFS achieved with targeted therapies have led to investigations into the optimal use of these agents, with a view to achieving the best possible prolongation of life for patients with advanced RCC. Efforts to optimize the use of targeted therapies have resulted in the widespread use of such agents sequentially. Nevertheless, the optimal sequence of targeted agents is not currently known.

Until data from ongoing clinical trials evaluating different treatment sequences is available, clinicians should take into account efficacy data as well as patient and disease characteristics and drugs toxicity profile when making treatment decisions and considering whether to switch treatment and which treatment to switch to.

Taking into consideration all the above mentioned data, one reasonable option could be sequential VEGF inhibitors in the second-line setting and mTOR inhibitors in the third-line setting. However, patients who are refractory to first-line VEGF-inhibitor therapy, in terms of radiographic progression on the first restaging studies, could proceed with a second-line mTOR inhibitor. It may also be appropriate to proceed with a second-line mTOR inhibitor in patients who have experienced serious or potentially life-threatening toxicities with initial VEGF-inhibitors.

Finally, there is a need to identify reliable biomarkers of treatment resistance and/or treatment response in order to select the most appropriate treatment for each patient.

Conflict of interest statement

The authors declare no conflict of interest.

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Adrenal incidentalomas in cancer patients are not always “innocent”: Report of a case and literature review

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ABSTRACT

Herein, we report the unusual case of a 78-year old woman with synchronous presentation of sigmoid cancer and a non-functioning primary adrenal cortex carcinoma, who developed superior vena cava syndrome due to metastatic lymphadenopathy from the latter malignancy. Our case suggests that adrenal incidentalomas during initial staging evaluation after cancer diagnosis are not always “innocent” and should not be *a priori* considered incidental findings attributed to hyperplasia, adenoma or even considered a non life-threatening metastasis from the primary tumor. It also emphasizes the importance of a continuous assessment of patients with synchronous primary malignancies, in order to timely evaluate changes in clinical or biological behavior and administer the appropriate treatment.

Key words: adrenal incidentaloma; primary carcinoma of the adrenal cortex; colon cancer; superior vena cava syndrome; Ki-67 mitotic index.

INTRODUCTION

Primary carcinoma of the adrenal cortex (ACC) is a rare and highly aggressive malignancy, accounting for an estimated 0.02% of all cancers [1]. Approximately 60% of ACCs are hormonally active, presented clinically as Cushing syndrome (in glucocorticoid excess), virilization (in androgen excess), or hypokalemia (in mineralocorticoid excess). In contrast, hormonally inactive ACCs usually present with abdominal discomfort (nausea, vomiting and abdominal fullness) or back pain caused by a mass effect of a large tumor [2]. Data from case series indicates that the majority of patients with ACC present with regional or distant spread; common sites of metastasis involve the liver, lungs, distant lymph nodes and bone [3].

ACC accounts for <5% of all adrenal lesions detected incidentally on radiographic imaging, referred to as ‘adrenal incidentalomas’ [4]. In patients with malignancy, the approach to incidentaloma is more critical because several malignant neoplasms have the tendency to metastasize to the adrenal glands, the most notorious being non-small-cell lung cancer. In this setting, distinction between metastasis, benign adrenal lesions or primary ACC is difficult with CT or MRI imaging [5-6]. Herein,

we present an unusual case of a patient with colon cancer presented with an adrenal incidentaloma on pre-operative imaging that proved to be a non-functional ACC.

CASE REPORT

A 78-year-old female was referred to our institution after synchronous resection of cancer of the sigmoid colon and a left adrenal lesion. The patient initially sought evaluation at a local clinic with a 2-month history of change in bowel movements, blood in the stool and abdominal pain. She had no remarkable medical history and was under no medications at the time. A colonoscopy performed at the same institution revealed a hemorrhagic mass measuring 5cm at the sigmoid region; subsequent biopsy revealed a moderately differentiated adenocarcinoma. Pre-operative staging including a computed tomography (CT) scan of the abdomen, revealed a 13.5x8.5x7.6cm adrenal mass with heterogeneous enhancement. A whole-body positron emission tomography (PET)/CT scan was performed, showing significant ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) uptake in the sigmoid colon and the left adrenal gland. No additional sites with increased uptake were identified.

Since ^{18}F -FDG-PET scan suggested malignant potential of the adrenal lesion, a synchronous resection of both the sigmoid and the adrenal lesion was opted. By virtue of the unknown origin of the adrenal mass, a thorough endocrine analysis, as proposed by the European Network for the Study of Adrenal Tumors (ENSAT) [7], was made prior to resection. Blood pressure and potassium levels were within normal limits. Serum glucose, plasma ACTH and dexamethasone suppression test, measured to assess glucocorticoid excess, were also within normal range. Determination of metanephrines in the urine excluded the presence of a pheochromocytoma. Due to the patient's hirsutism, serum dehydroepiandrosterone sulfate (DHEA-S) was also measured, which was within the normal limits. Sigmoidectomy and locoregional lymph node dissection revealed a stage IIIB (T3N1M0) adenocarcinoma of the colon (Figure 1), while resection of the adrenal mass disclosed a stage III (T3N0M0) adrenal carcinoma with Weiss score [8] of 4, a mitotic rate of 10 per 50 high power fields (HPF), atypical mitoses and capsular invasion (Figure 2 A, B, C). Immunohistochemical analysis of the biopsy specimens revealed a positive staining for synaptophysin (Figure 3A) and Ki-67 mitotic index (15% - Figure 3B). Tumor markers, including CEA and CA-19-9 were within normal limits.

At that time, the patient was referred to our institution for further evaluation and treatment. Given the absolute benefit offered by adjuvant chemotherapy in patients with stage III colon cancer [9], whereas data regarding the use of mitotane in the adjuvant setting of ACC is still controversial [3], she received adjuvant chemotherapy with the FOLFOX regimen (Oxaliplatin 85mg/m², Leucovorin 200mg/m², 5-FU 400mg/m² bolus, 5-FU 600mg/m² continuous infusion for 46 hours). After 2 months (8 cycles) of treatment, the patient was re-evaluated with CT imaging of the chest and abdomen, which indicated a new 17mm nodular mass in the azygoesophageal recess and enlarged right lower paratracheal lymph nodes. We decided to perform both a biopsy of the mass in the azygoes-

Figure 1.

Adenocarcinoma of the colon, 100 x magnification.

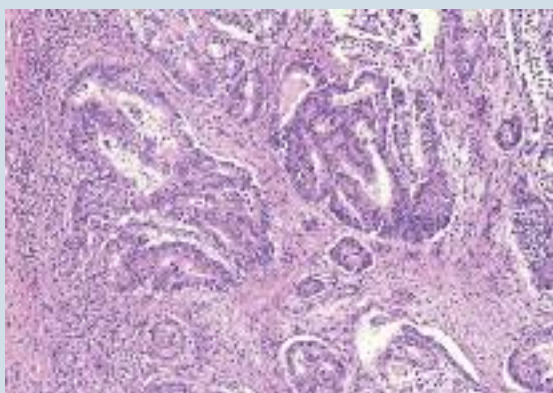
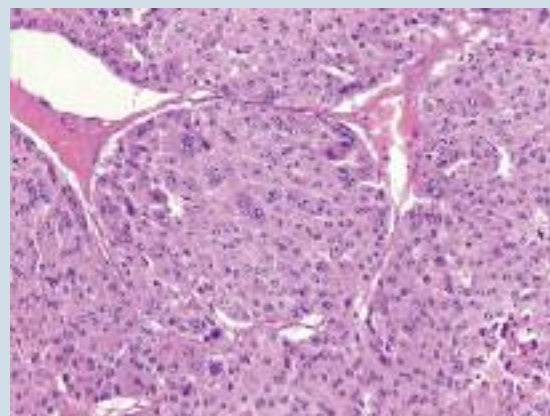


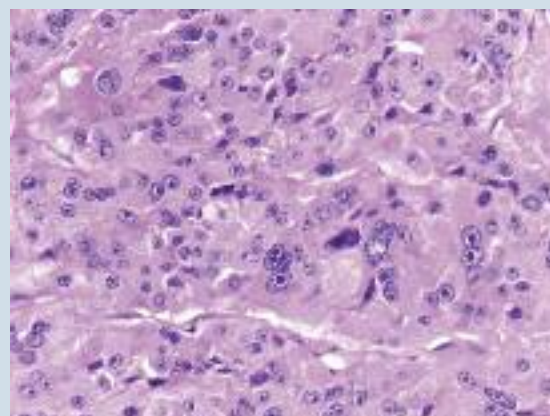
Figure 2.

Adrenal carcinoma

A: 200 x magnification.



B: Pathologic view showing atypical mitoses, 400 x magnification.



C: Pathologic view demonstrating capsular invasion, 100 x magnification.

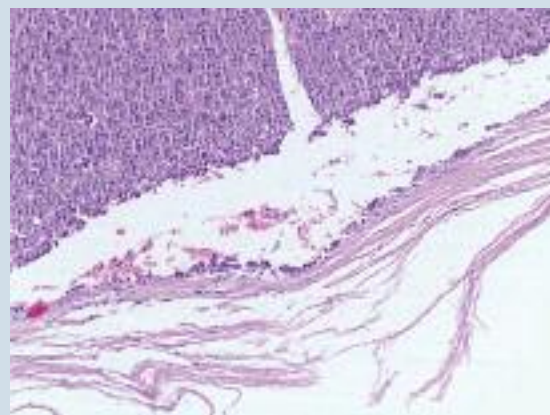
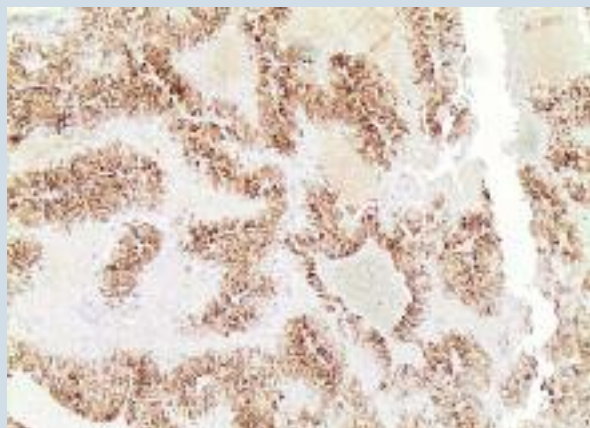


Figure 3.

Immunohistochemical staining.

A: Synaptophysin positivity.



B: Positivity for mitotic index Ki-67%.



phageal recess and of the lower paratracheal lymph node mass, in order to identify the site of origin. Biopsy of both lesions suggested ACC as the primary origin of the lymph node involvement. Consequently, first-line treatment for advanced ACC was started consisting of cisplatin 40mg/m², adriamycin 40mg/m², etoposide 100mg/m², and oral mitotane initially at a dose of 2g/day with continuous dose monitoring; hydrocortisone replacement therapy 50mg/day was added. During treatment with mitotane, full blood count, liver function tests, ACTH, thyroid hormones, cholesterol and renin were regularly measured. The drug was well tolerated and gradually increased to a final dose of 12g/day. Chemotherapy was discontinued after 6 cycles, due to platinum-related sensorineural hearing loss and retinal detachment, for which she was successfully treated with vitrectomy, resulting in gradual vision gain. Of note, re-evaluation after completion of 3 cycles of chemotherapy, showed disease stabilization (modified RECIST criteria).

Three months after cessation of chemotherapy, the patient presented at the emergency room with worsening dyspnea, swelling of the face and neck and dilation of veins on her upper chest. Electrocardiogram indicated paroxysmal atrial fibrillation (AF). The patient also underwent a CT scan of the chest, which revealed enlargement of the paratracheal nodes with signs of superior vena cava obstruction. The patient underwent chemical cardioversion of the AF, while administration of mitotane was reduced progressively. She was promptly started on conventional radiotherapy, which resulted in shrinkage of lymph nodes size and subsequent improvement of respiratory distress and facial edema. One month after completion of radiotherapy, second-line chemotherapy with weekly paclitaxel was administered, while mitotane treatment was stopped. After completion of 6 weeks of therapy, further partial response in the mediasti-

num was noted. After 4 more cycles of paclitaxel treatment, the patient developed abdominal pain. CT imaging of the abdomen performed at that time showed deterioration with evidence of malignant peritoneal implantations. The case was discussed at the multidisciplinary oncology meeting; CT-guided needle aspiration biopsy of peritoneal lesions was proposed in order to define the origin of peritoneal carcinomatosis, but the patient refused to undergo the procedure. It was thus decided that treatment at that point should aim primarily at colon cancer, since peritoneal disease was more likely to represent a manifestation of colon rather than adrenal cancer. She was started on modified FOLFIRI-Bevacizumab regimen (Irinotecan 180mg/m², Leucovorin 200mg/m², 5-FU bolus 400mg/m², 5-FU infusional 600mg/m² and bevacizumab 5mg/kg). Thus far, she has received 2 cycles of chemotherapy with clinical benefit, as defined by elimination of abdominal pain.

DISCUSSION

Herein, we describe an unusual case of ACC initially presented as an incidentaloma in a patient with colon cancer, which progressively displayed a metastatic behavior causing superior vena cava syndrome and upper airway obstruction.

Adrenal incidentalomas in cancer patients are not always "innocent"; ACC accounts for approximately 5% of adrenal incidentalomas [4]. However, in the majority of patients with malignancy, adrenal incidentalomas most commonly represent sites of metastases of the primary tumor or benign adrenal adenomas [10]. Furthermore, synchronous existence of colorectal and adrenal carcinoma is relatively uncommon. In two case series reported by a Chinese group that included 4 patients undergoing synchronous resection of colorectal cancer and adrenal lesion, a diagnosis of ACC was made in a single patient [11-12]. Moreover, numerous

case series report on the pathological diagnosis and outcome of patients with malignancy undergoing adrenalectomy for incidentaloma: In a study evaluating the role of imaging and surgery in 42 patients with cancer, including colon cancer and adrenal lesions, none of the patients was found to have an ACC [13]. Similarly, in two series of a limited number of patients with malignancy subjected to laparoscopic adrenalectomy, no case of ACC was reported [14-15]. Moizandeh *et al.* have reported a pathological diagnosis of ACC in 6/31 patients with malignancy, although the site of the coexisting tumor in patients with ACC is not clearly mentioned in the study [16]. However, in the majority of these studies, adrenal masses were discovered during follow-up for the primary malignancy, which does not allow direct comparison with the case of our patient.

Superior vena cava syndrome (SVC) is considered a medical emergency; in few cases treatment can be delayed, until a histological diagnosis is obtained. In the case of our patient, histopathological diagnosis was made before superior vena cava was compressed by the increasing size of the mediastinal lymph nodes. Although regional lymph node metastasis is encountered in 24% of patients with ACC, metastasis to mediastinal lymph nodes is rare [3]. SVC syndrome directly related to metastatic ACC has been reported only once in the literature [17]. The patient was treated with radiation, since ACC is not considered a chemosensitive tumor; chemotherapy with cisplatin, adriamycin and etoposide had already been administered to our patient without evidence of objective response.

The choice of treatment in a patient with two synchronous cancers is a difficult task. We selected to treat the patient with adjuvant chemotherapy for her colon cancer, considering the

high risk of relapse to stage III colon cancer [9]. On the other hand, there is an ongoing debate as to whether patients benefit from adjuvant mitotane in ACC. In patients with localized ACC and R0 resection, adjuvant therapy is suggested if mitotic index Ki67 is >10% and tumor size is >8cm [7]. In the case of our patient, Ki67% was 20% and tumor size 13.5cm in major dimension, but the risk for developing distant metastases was statistically higher for colon cancer than for ACC and the hypothetical combination of the two regimens was expected to be highly toxic, particularly in terms of myelosuppression. It is unclear at the moment whether administration of adjuvant mitotane would confer any substantial clinical benefit. Nevertheless, once the diagnosis of metastatic ACC was established, adjuvant chemotherapy for colon cancer was discontinued and first-line chemotherapy for the advanced ACC was initiated. Given the rarity of the tumor and the paucity of clinical trials, second-line chemotherapy for ACC (weekly paclitaxel) was chosen based on published case series [18, 19]. In conclusion, we report an unusual case of a patient with synchronous presentation of non-functioning ACC and colon cancer, who developed SVC syndrome due to metastases from ACC. Our case suggests that adrenal incidentalomas are not always "innocent" and should not be *a priori* considered incidental findings related to hyperplasia or adenoma. It also emphasizes the importance of a continuous assessment of patients with synchronous primary malignancies, in order to timely evaluate changes in clinical or biological behavior and administer the appropriate treatment.

Conflict of interest statement

The authors declare no conflict of interest.

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Key Words: 5-10, for indexing purposes.

Introduction: Provides a context or background for the study (that is, the nature of the problem and its significance) and states the specific purpose or research objective of, or hypothesis tested by, the study or observation.

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Results: This section presents results in logical sequence in the text, tables, and illustrations, giving the main or most

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Πίνακας 2: Αναμενόμενες ενέργειες σε ασθενείς με προχωρήσαντα μελάνομα που έλαβαν YERVOY 3 mg/kg (n = 767)*	
Λοιμώξεις και παροξυσμοί	
Οχι συχνές	σηψαιμία [†] , σηπτική καταπληξία [†] , μηνιγγίτιδα, γαστρεντερίτιδα, εκκολιμνωτίτιδα, ουρολοιμώξη, λοίμωξη του ανώτερου αναπνευστικού συστήματος, λοίμωξη του κατώτερου αναπνευστικού συστήματος
Νεφροπάθειες, καλοήγη και μη καθορισμένα (περιλαμβανόμενα κύστες και πολύποδες)	
Συχνές	πόνος από όγκο
Οχι συχνές	παρανεφροπλασματικό σύνδρομο
Διαταραχές του αιμοποιητικού και του λεμφικού συστήματος	
Συχνές	αναιμία, λευκοπενία
Οχι συχνές	αιμολυτική αναιμία [†] , θρομβοπενία, ησιανοφιλία, ουδετεροπενία
Διαταραχές του ανοσοποιητικού συστήματος	
Οχι συχνές	υπερευαίσθησια
Διαταραχές του ενδοκρινικού συστήματος	
Συχνές	υποϋποφισιασμός (συμπεριλαμβάνεται η υποφυσίτιδα [†]), υποθυρεοειδισμός [†]
Οχι συχνές	επινεφριδιακή ανεπάρκεια [†] , υπερθυρεοειδισμός [†] , υπογοναδισμός
Διαταραχές του μεταβολισμού και της θρέψης	
Πολύ συχνές	μειωμένη όρεξη
Συχνές	αφυδάτωση, υποκαλιαιμία
Οχι συχνές	υπονατρίαιμία, αλκαλωση, υποφωσφοραμία, σύνδρομο λύσης όγκου
Ψυχιατρικές διαταραχές	
Συχνές	συχυρτική κατάταση
Οχι συχνές	μεταβολές της νοητικής κατάστασης, κατάθλιψη, μειωμένη γενετήσια ορμή
Διαταραχές του νευρικού συστήματος	
Συχνές	περιφερική αισθητική νευροπάθεια, ζάλη, κεφαλαλγία, λήθαργος
Οχι συχνές	σύνδρομο Guillain-Barré [†] , σπαστική, κρανική νευροπάθεια, εγκεφαλικό οίδημα, περιφερική νευροπάθεια, στασία, τρόμος, μυϊκόλκνος, δυσαρθρία
Οφθαλμικές διαταραχές	
Συχνές	θαμνή όραση, πόνος του οφθαλμού
Οχι συχνές	ραγοειδίτιδα [†] , αιμορραγία του υαλοειδούς σώματος, ιρίτιδα [†] , μειωμένη οπτική οξύτητα, αίσθημα ξένου σώματος στους οφθαλμούς, επιπεφυκίτιδα
Καρδιακές διαταραχές	
Οχι συχνές	αρρυθμία, κοιλική μαρμαρυγή
Αγγειακές διαταραχές	
Συχνές	υπόταση, εξάψη
Οχι συχνές	αγγειίτιδα, αγγειοπάθεια [†] , περιφερική ισχαιμία, ορθοστατική υπόταση
Διαταραχές του αναπνευστικού συστήματος, του θώρακα και του μεσοθωρακίου	
Συχνές	δυσπνοια, ρίγχος
Οχι συχνές	αναπνευστική ανεπάρκεια, σύνδρομο οξείας αναπνευστικής δυσχέρειας [†] , διήθηση πνεύμονα, πνευμονικό οίδημα, πνευμονίτιδα, αλλεργική ρινίτιδα
Διαταραχές του γαστρεντερικού	
Πολύ συχνές	διάρροια [†] , έμετος, ναυτία
Συχνές	γαστρεντερική αιμορραγία, κοιλίτιδα [†] , δυσκοιλιότητα, γαστροοισοφαγική παλινδρόμηση, κοιλιακό άλγος
Οχι συχνές	έντερρο του γαστρεντερικού σωλήνα [†] , διάρρηξη του παχέος εντέρου [†] , διάρρηξη του εντέρου [†] , περιτονίτιδα [†] , παγκρεατίτιδα, διατεταμένο, γαστρικό έλκος, έλκος του παχέος εντέρου, οισοφαγίτιδα, ελίκος [†]
Διαταραχές του ήπατος και των χοληφόρων	
Συχνές	μη φυσιολογική ηπατική λειτουργία
Οχι συχνές	ηπατική ανεπάρκεια [†] , ηπατίτιδα, ηπατομεγαλία, ίκτερος
Διαταραχές του δέρματος και του υποδόριου ιστού	
Πολύ συχνές	εξάνθημα [†] , κνησμός [†]
Συχνές	δερματίτιδα, ερυθρίδα, λεύκη, κνίδωση, αλωπεκία, κυκλική ιδρώδης, ξηροδερμία
Οχι συχνές	τοξική επιδερμική νεκρόλυση [†] , λευκοκυτταροκλαστική αγγειίτιδα, αποβολή του δέρματος
Διαταραχές του μυοσκελετικού συστήματος και του συνδετικού ιστού	
Συχνές	αρθραλγία, μυαλγία, μυοσκελετικός πόνος, μυϊκοί σπασμοί
Οχι συχνές	ρευματική πολυμυαλγία, αρθρίτιδα [†]
Διαταραχές των νεφρών και των ουροφόρων οδών	
Οχι συχνές	νεφρική ανεπάρκεια [†] , σπειραματονεφρίτιδα [†] , νεφρική σωληναριακή οξείωση
Διαταραχές του αναπαραγωγικού συστήματος και του μαστού	
Οχι συχνές	αμηνόρροια
Γενικές διαταραχές και καταστάσεις της οδού χορήγησης	
Πολύ συχνές	κόπωση, αντίδραση της θέσης ένεσης, πυρεξία
Συχνές	ρίγη, εξάθνηση, οίδημα, άλγος
Οχι συχνές	πολυοργανική ανεπάρκεια [†] , σχετιζόμενη με την έγχυση αντίδραση
Παρακλινικές εξετάσεις	
Συχνές	αυξημένη αμινοτρανσφεράση της αλανίνης [†] , αυξημένη ασπαρτική αμινοτρανσφεράση [†] , αυξημένη χοληρυθρίνη αίματος, μειωμένο σμακτικό βάρος
Οχι συχνές	μη φυσιολογικές δοκιμασίες ηπατικής λειτουργίας, αυξημένη κρεατινίνη αίματος, αυξημένη θυρεοειδοτρόπος ορμόνη αίματος, μειωμένη κορτιζόλη αίματος, μειωμένη κορτικοτροπίνη αίματος, αυξημένη λιπασή, αυξημένη αμιλάση αίματος [†] , μειωμένη ταχύτερη όραση αίματος

α) συνηθισμένες βασιλίσσας σε συγκεκριμένα στάδια από 9 κλινικές δοκιμές που εξετάζουν το YERVOY 3 mg/kg δόση σε μεθάνια.

β) Συμπτωματολόγηση ή θανατηφόρος έκβαση.

γ) Πρόσβατες πληρωμένες σχετικά με αυτές τις πιθανές φλεγμονώδεις ανεπιθύμητες ενέργειες παρατίθενται στην «Περιγραφή ανεπιθύμητων ενεργειών» και την παράγραφο 4.4. Τα δεδομένα που παρουσιάζονται σε αυτές τις παραγράφους αποτυπώνουν κυρίως την εμπειρία από μια μέληθος Φάσης 3, την MDX01020.

δ) Αναφορές σε πρόσφατες μελέτες εκτός των ολοκληρωμένων κλινικών δοκιμών στο μεθάνια.

Πρόσβατες ανεπιθύμητες ενέργειες που δεν αναφέρονται στον Πίνακα 2 έχουν αναφερθεί σε ασθενείς που έλαβαν άλλες δόσεις ($c_{itc} < 3$ mg/kg) YERVOY σε κλινικές δοκιμές μεθάνια. Αυτά οι πρόσβατες αναφέρονται παρακάτω ανά τις συνηθισμένες < 1%: μηνιγγίτις, μυοκαρδίτις, καρδιομυοπάθεια, αντανόηση πηλατίου, πολυμορφο ερύθημα, αντανόηση νεφρίτις, αντανόηση οφθαλμολογία με μυστηριώδη βλάβη, αντανόηση υπερτροφική, υπερτροφική αντανόηση, δευτερογενής αντανόηση του φλοιού των επινεφριδίων, αντανόηση υπερτροφική, θυρεοειδής, επεκτατική, βλακώδης, βλάβη του ορθού, σκληρίτις, καταρράκτης αρτηρίτις, φανόνημα Raynaud, πικρικό, αντανόηση, παλαμπάκη, αντανόηση ερυθροδερμική, ψωρίαση, αιματοχρωμία, πρωτεϊνωσία, οίδημα θυρεοειδούς, οφθαλμολογία οφθαλμολογία, μυστηριώδη βλάβη, μυστηριώδη βλάβη, λευκοπενία και πολυκυστία. Περιγραφή επιβεβαιωμένων ανεπιθύμητων ενεργειών: Με εξαίρεση τις περιπτώσεις στις οποίες επισημειώθηκε, τα δεδομένα για τα παρακάτω επιβεβαιωμένες ανεπιθύμητες ενέργειες βασίζονται σε ασθενείς που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg ($n = 131$) ή YERVOY 3 mg/kg σε συνδυασμό με τη δόση ($n = 380$) σε μια μέληθος Φάσης 3 που προεργασμένο (ή μη προεργασμένο ή μεταστατικό) μεθάνια (MDX01020, βλ. παράγραφο 5.1). Οι καταγεγραμμένες γραμμές για την αντιμετώπιση αυτών των ανεπιθύμητων ενεργειών περιγράφονται στην παράγραφο 4.4. Γαστρεντερικές αντανόησης που συνδέονται με το αντανόηση. Το YERVOY σχετίζεται με σοβαρές γαστρεντερικές αντανόησης που συνδέονται με το αντανόηση. θανατηφόρα πεπτικά ή/και διάρρηξη του γαστρεντερικού σωλήνα έχουν αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με τη δόση. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε διάρροια και κόπωση/απώλεια βάρους στο 27% και το 8% αντίστοιχα. Η συχνότητα οφθαλμολογίας (βαθμίου 3 ή 4) διάρρηξη και οφθαλμολογίας (βαθμίου 3 ή 4) κόπωση ήταν 5% για το καθεστώς. Ο διάμεσος χρόνος έως την εκδήλωση οφθαλμολογίας ή θανάτου (βαθμίου 3 έως 5) γαστρεντερικών αντανόησης που συνδέονται με το αντανόηση ήταν 8 εβδομάδες (έκρος 5 έως 23 εβδομάδες) από την αρχή της θεραπείας. Με καταγεγραμμένες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο ή υποχώρηση παρουσιάζονται στις περισσότερες περιπτώσεις (90%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση (ορίστηκε ως βελτίωση σε μία [βαθμίου 1] ή καλύτερη ή σταθεροποίηση κατά την έναρξη) 4 εβδομάδες (έκρος 0,6 έως 22 εβδομάδες). Σε κλινικές δοκιμές η κόπωση που συνδέεται με το αντανόηση συσχετίζεται με στοιχεία φλεγμονής του βλεννογόνου, με ή χωρίς εξέλκωση και λευκοκυτταρίτιδα και ουδετεροφιλική διάφραση. Ηπατοκυτταρική που συνδέεται με το αντανόηση. Το YERVOY σχετίζεται με σοβαρή ηπατοκυτταρική που συνδέεται με το αντανόηση. θανατηφόρα ηπατική ανεπάρκεια έχει αναφερθεί σε < 1% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg. Αλυσή της AST και της ALT υποχώρησης βάρους αναφέρθηκε στο 1% και τα 2% των ασθενών αντίστοιχα. Δεν υπήρξαν αναφορές (βαθμίου 3 ή 4) αύξηση της AST ή της ALT. Ο χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανάτου (βαθμίου 2 έως 5) ηπατοκυτταρικής που συνδέεται με το αντανόηση κυμαίνεται από τις 3 έως 9 εβδομάδες από την αρχή της θεραπείας. Με καταγεγραμμένες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, ο χρόνος έως την υποχώρηση κυμαίνεται από 0,7 έως 2 εβδομάδες. Σε κλινικές δοκιμές, βίαιος πόνος από ασθενείς που είχαν ηπατοκυτταρική σχετιζόμενη με το αντανόηση, εμφανισμένα στοιχεία όξιας φλεγμονής (ουδετερόφιλια, λευκοκυτταρίτιδα και μορφολογία), δερματικές ανεπιθύμητες αντανόησης που συνδέονται με το αντανόηση. Το YERVOY σχετίζεται με σοβαρές δερματικές ανεπιθύμητες αντανόησης που μπορεί να συνδέονται με το αντανόηση. θανατηφόρος τοξική επιδερμική νεκρόλυση έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με τη δόση (παρ. 100) (παρ. 100) (παρ. 5.1). Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, αναφέρθηκε εξάνθημα και κνηρίος δερματοεπιδερμική βλάβη, το καθεστώς στο 27% των ασθενών. Εξάνθημα και κνηρίος επάγονται από YERVOY ήταν κυρίως ήπιος (βαθμίου 1) ή μέτριος (βαθμίου 2) και ανταποκρίθηκαν σε συμπτωματική θεραπεία. Ο διάμεσος χρόνος έως την εκδήλωση μέτριας έως σοβαρής ή θανάτου (βαθμίου 2 έως 5) δερματικών ανεπιθύμητων αντανόησης ήταν 3 εβδομάδες από την αρχή της (έκρος 0,9 έως 16 εβδομάδες). Με καταγεγραμμένες γραμμές για την αντιμετώπιση σχετιζόμενες με το πρωτόκολλο, υποχώρηση παρουσιάζονται στις περισσότερες περιπτώσεις (87%), με διάμεσο χρόνο από την εκδήλωση έως την υποχώρηση 5 εβδομάδες (έκρος 0,6 έως 29 εβδομάδες). Νευρολογικές ανεπιθύμητες αντανόησης που συνδέονται με το αντανόηση. Το YERVOY σχετίζεται με σοβαρές νευρολογικές αντανόησης που συνδέονται με το αντανόηση. θανατηφόρο σύνδρομο Guillain-Barre έχει αναφερθεί σε < 1% των ασθενών που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με τη δόση. Συμπτώματα οφθαλμολογίας με μυστηριώδη βλάβη έχουν αναφερθεί σε < 1% των ασθενών που έλαβαν υψηλότερες δόσεις YERVOY σε κλινικές δοκιμές. Ενδοκρινολογικές που συνδέονται με το αντανόηση. Στην ομάδα με μονοθεραπεία με YERVOY 3 mg/kg, υποσηπτική οφθαλμολογία βλάβη αναφέρθηκε στο 4% των ασθενών. Επιπρόσθετες ανεπάρκειες, υπερθυρεοειδισμός και υπερθυρεοειδισμός οφθαλμολογία αναφέρθηκε το καθεστώς στο 2% των ασθενών. Η συχνότητα οφθαλμολογίας (βαθμίου 3 ή 4) υποσηπτική οφθαλμολογία στο 3% των ασθενών. Δεν υπήρξαν αναφορές οφθαλμολογίας ή πόλο οφθαλμολογίας (βαθμίου 3 ή 4) επιπρόσθετες ανεπάρκειες, υπερθυρεοειδισμός ή υπερθυρεοειδισμός. Ο χρόνος έως την εκδήλωση μέτριας έως πόλο οφθαλμολογίας (βαθμίου 2 έως 4) σχετιζόμενες με το αντανόηση ενδοκρινολογικές κυμαίνεται από 7 έως περίπου 20 εβδομάδες από την αρχή της θεραπείας. Ενδοκρινολογική σχετιζόμενη με το αντανόηση και παρατηρήθηκαν σε κλινικές δοκιμές, ήταν γενικώς ελαφρώς με θεραπεία υποκατάστασης ορμόνων. Άλλες ανεπιθύμητες αντανόησης που συνδέονται με το αντανόηση. Ο παρακάτω επιβεβαιωμένες αντανόησης που πιθανολογείται ότι συνδέονται με το αντανόηση, έχουν αναφερθεί σε < 2% των ασθενών που έλαβαν μονοθεραπεία με YERVOY 3 mg/kg: ραγδαία, μυοκαρδίτις, αύξηση λίπιδων και υπερτασμογονία. Επιπρόσθετες, κίρση, αμυλοτική αμυloid, αύξηση αμυloid, πολυκυστική ανεπάρκεια και πνευμονική έχουν αναφερθεί σε ασθενείς που έλαβαν YERVOY 3 mg/kg σε συνδυασμό με πεπτικό βίαιος πόνο (παρ. 100). YERVOY 5 mg/ml πηλατίου δόση για παρασκευή διαλύματος προς έγχυση – Συσκώσιμος: 1 Φιάλδιο (γυάλινο) x 10 ml με ενδεικτική Νοοκωμική 3.1 3.887,16 €, ενδεικτική Χονδρική τιμή 4.468,00 € και ενδεικτική YERVOY 5 mg/ml πηλατίου δόση για παρασκευή διαλύματος προς έγχυση – Συσκώσιμος: 1 Φιάλδιο (γυάλινο) x 40 ml με ενδεικτική Νοοκωμική 3.1 15.548,65 €, ενδεικτική Χονδρική τιμή 17.872,01 €.

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Το YERVOY™ (ipilimumab) ενδείκνυται για τη θεραπεία του προχωρημένου (ανεγχείρητου ή μεταστατικού) μελανώματος σε ενήλικους 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

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*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.

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