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Review: Side Effects of Approved Molecular Targeted Therapies in Solid Cancers

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Key Words. Targeted therapy • Toxicity • Anti-EGFR agents • Anti-HER-2 agents • Anti-VEGFR agents

Disclosure: No potential conflicts of interest were reported by the authors, planners, reviewers, or staff managers of this article.

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. List the molecular targeted agents that are considered standard practice in solid tumors.
2. Differentiate among the side effects of commonly used molecular targeted agents.
3. Better characterize the side effects of molecular targeted agents.

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ABSTRACT

Major advances have been achieved in the field of biologically based therapies for cancer in the last few years, and some of the recently approved molecular-targeted therapies are now being used in daily clinical practice. These molecular targets are also expressed in normal cells, which explains the different grades of toxicity, resulting from the disruption of normal cellular function. In general, targeted molecular therapies have good toxicity profiles, but some patients are exquisitely sensitive to these drugs and can develop particular and severe toxicities. In this article, we review the toxicity and safety of various small molecules and monoclonal antibodies used in solid tumors, with discussion of the pathophysiology, correlation with response, and strategies for prevention and management. ***The Oncologist*** 2007;12:1443–1455

INTRODUCTION

The concept of targeted therapy is derived from the idea of a "magic bullet," first elaborated by Paul Erlich in the late 1800s, when he described a chemical with the ability to specifically target microorganisms [1]. One century later, progress in molecular biology contributed to the increasing understanding of the underlying mechanisms related to cancer initiation, promotion, and progression. As a con-

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Table 1. Main molecular targeted agents in the treatment of solid cancers

Drug	Class	Mechanism of action
Gefitinib	Small molecule (anilinoquinazoline)	TK inhibitor of EGFR
Erlotinib	Small molecule (quinazoline)	TK inhibitor of EGFR
Cetuximab	Monoclonal antibody (ch IgG_1)	Block EGFR
Panitumumab	Monoclonal antibody (hu IgG_1)	Block EGFR
Trastuzumab	Monoclonal antibody (hu IgG_1)	Block HER-2
Lapatinib	Small molecule	Inhibition of EGFR and HER-2
Bevacizumab	Monoclonal antibody (hu IgG_1)	Block VEGF
Sorafenib (BAY 43–9006)	Small-molecule multitargeted TK inhibitor	Inhibition of VEGFR-2, VEGFR-3, PDGFR-B, Raf, c-Kit, and Flt-3
Sunitinib (SU 11248)	Small-molecule multitargeted TK inhibitor	Inhibition of VEGFR, PDGFR, cKit, and Flt-3

All of these agents are in clinical practice or in phase III clinical development.
Abbreviations: ch, chimeric; EGFR, epidermal growth factor receptor; HER-2, human epidermal growth factor receptor 2; hu, human; PDGFR, platelet-derived growth factor receptor; TK, tyrosine kinase; VEGF, vascular endothelial growth factor.

sequence, monoclonal antibodies (mAbs) and small molecules have been developed. These drugs interfere with a specific molecular target (typically a protein) involved in tumor growth and progression, and therefore have become an important part of the anticancer armamentarium [2]. These targets include growth factor receptors, signaling molecules, cell-cycle proteins, modulators of apoptosis, and molecules involved in invasion and angiogenesis, which are essential for development and homeostasis in normal tissues. In cancer cells, they have a gain of function as a consequence of overexpression and/or gene alterations. Despite the high selectivity of these novel targeted therapies, a range of previously unknown and sometimes unpredictable side effects can emerge.

Most of these side effects are directly related to the specific molecular target in normal tissues inhibited or modulated by the specific drug. The paradigm of this phenomenon is the cutaneous toxicity observed with the inhibitors of the epidermal growth factor receptor (EGFR), such as erlotinib (Tarceva®; Genentech, Inc., South San Francisco, CA), gefitinib (Iressa®; AstraZeneca Pharmaceuticals, Wilmington, DE), panitumumab (Vectibix®; Amgen Inc., Thousand Oaks, CA), and cetuximab (Erbitux®; ImClone Systems, Inc., New York), commonly used in advanced colorectal and lung cancer, as well as the dual inhibitor of EGFR and human epidermal growth factor receptor (HER)-2, lapatinib (Tykerb®; GlaxoSmithKline, Philadelphia). The EGFR is involved in proliferation, survival, and differentiation [3], and in the skin, the EGFR and its ligands are important in the cycle of keratinocyte maturation [4]. So, as a result of EGFR inhibition, a typically papulopustular [5] eruption is observed in most patients treated with this family of anti-EGFR agents. The main molecular targeted agents in the treatment of solid cancers currently tested in phase III trials are detailed in Table 1.

mAbs were first generated by Köhler and Milstein [6] in 1975, using a technique of somatic cell hybridization. In early clinical trials, these mAbs of murine origin resulted in common immunogenicity responses, leading to the production of human anti-mouse antibodies (HAMAs). To avoid this immunogenicity and to increase the activity of the mAbs, new chimeric and humanized mAbs were generated by biotechnology. A good example of this is trastuzumab, an anti-HER-2 humanized recombinant mAb with excellent efficacy in breast cancer, and very few side effects related to its murine component. These clinical reactions are described as a flu-like syndrome with fever and chills that appears in 40% of patients, mainly at the first drug infusion.

Small molecules, such as tyrosine kinase inhibitors (TKIs), are less specific than therapeutic mAbs [7], and some of them can inhibit multiple targets simultaneously, including cell receptors or signal transduction pathway proteins, leading to a higher risk for toxicity [8]. In addition, it is anticipated that small molecule TKIs present more gastrointestinal symptoms, in part as a result of their oral formulation. Indeed, the risk for unusual side effects is greater when these molecular targeted therapies are used in combination with conventional cytotoxic chemotherapy or when mAbs are combined with small molecule TKIs.

The scope of this review is to describe the different side effects associated with novel targeted therapies for solid cancer that have been used recently in large studies or have started being used in clinical practice. It discusses the underlying pathogenesis of these adverse reactions with suggestions on how to predict, prevent, and circumvent such toxicities.

Side Effects of Anti-EGFR Therapies

Cell surface receptors are involved in the transmission of several different extracellular signals, such as environmental stresses, growth factors, neuropeptides, or hormones, to the cell nucleus, thus participating in the regulation of a large diversity of signaling pathways and cell responses, including cell proliferation and death. The EGF, or ErbB, family of receptors comprises one of these types of surface receptor, and consists of four members: EGFR or ErbB-1, HER-2/neu or ErbB-2, HER-3 or ErbB-3, and HER-4 or ErbB-4, all of them (except HER-3) with a TK domain in the intracellular part of the receptor responsible for the phosphorylation of downstream signaling proteins. Among the main EGFR ligands, we have EGF, transforming growth factor α, betacellulin, heparin-binding EGF-like growth factor, amphiregulin, and epiregulin. After binding to the ligand, homodimerization of EGFR or heterodimerization of EGFR with other members of the ErbB family occurs [9, 10]. EGFR and its ligands have an important role in the regulation of epithelial cell proliferation, survival, and differentiation during physiological development, particularly in the skin and in the gastrointestinal tract, as well as a key role in mesenchymal and neuronal tissue formation [11].

In the skin, EGFR activation is required for keratinocyte proliferation, survival, and motility and is also involved in the process of differentiation and keratinization [3]. Finally, activation of EGFR triggers mitogenic signaling in gastrointestinal mucosa and other tissues, having its expression upregulated in colon cancer, non-small cell lung cancer (NSCLC), and head and neck cancer, as a few examples [12]. EGFR is also responsible for the initiation of mitogenic intracellular signal cascades through its TK activity, and it has been related to neoplastic cell proliferation, migration, stromal invasion, resistance to apoptosis, and angiogenesis [13].

Currently, the main anti-EGFR therapies prescribed are cetuximab and panitumumab, two mAbs directed toward the extracellular ligand-binding domain of this receptor, and gefitinib and erlotinib, which are small molecules that inhibit the activation of the TK activity of the receptor. Cetuximab was first approved by the U.S. Food and Drug Administration (FDA) in 2004 for the treatment of advanced colorectal cancer, either in combination with irinotecan or as single-agent therapy, in patients refractory to or intolerant of irinotecan-based therapies. More recently, cetuximab has also been approved in combination with radiation for head and neck squamous cell carcinoma. Panitumumab was approved for the treatment of metastatic colorectal cancer in 2006, following standard chemotherapy. Gefitinib had its FDA approval for the treatment of patients with advanced NSCLC who had failed two or more lines of chemotherapy in 2003, and erlotinib obtained FDA consent in 2004, as a single agent, for the second- or third-line treatment of patients with locally advanced or metastatic NSCLC.

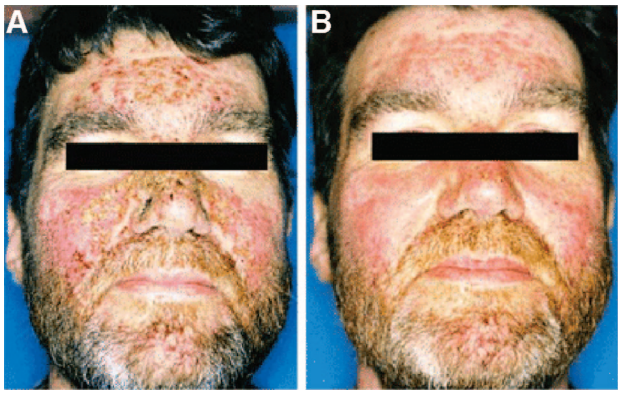

Figure 1. Cetuximab-induced acneiform rash before **(A)** and 1 week after **(B)** treatment (hydrocortisone/tararotene). From Moss JE, Burtness B. Cetuximab-associated acneiform eruption. N Engl J Med; 2005:353:e17, with permission.

Skin Toxicity

As predicted in preclinical toxicologic studies and also in knockout mice [3], the most commonly observed side effect with EGFR inhibitors is an acneiform eruption, also called acne-like rash or folliculitis, which occurs in 50%–100% of patients [14–16], which is more severe and diffuse with cetuximab (Fig. 1) than with small molecule TKIs, as shown in Table 2. Overall, the acneiform rash is characterized by erythematous follicular papules and pustules that appear in areas rich in sebaceous glands, such as the face, forehead, upper chest, and back, and can also affect the lower parts of the back and abdomen as well as the palms and soles [17–20]. In facial presentations, it can resemble rosacea or seborrheic dermatitis [21]. Usually, the acneiform eruption appears a few days after the start of the anti-EGFR treatment and is more intense at weeks 2 or 3 of treatment [22]. The folliculitis is dose dependent [15, 23, 24], and in most cases is present in mild and moderate grades, usually resolving a few weeks after treatment discontinuation without sequelae. Some spontaneous improvements have been seen without the need to stop treatment [16]. A postinflammatory hyperpigmentation state typically can be seen following the acneiform eruption. On microscopic evaluation, the skin lesions represent suppurative folliculitis [20, 21, 23] without comedone formation (typical from acne). Bacterial cultures of papules and pustules are classically negative [25].

Importantly, since anti-EGFR therapy is administered over long periods of time, adequate management of cutane-

Table 2. Incidence of acneiform eruption with epidermal growth factor receptor (EGFR) inhibitors

EGFR inhibitor	Any grade (%)	Grade 3 or 4 (%)
Cetuximab [14]		
Monotherapy	80	5.2
With irinotecan	80	9.3
Gefitinib		
50–100 mg/day [15]	53	65
150–1,000 mg/day [24]	1.6	2.2
Erlotinib [16, 113]		
150 mg/day	67–79	2.6–10.4
Panitumumab [36, 114]	70–100	10
Lapatinib [71]	38	3

ous side effects and prompt prescription of symptomatic measures improve the patient's quality of life and can improve adherence to treatment. General measures include maximal hydration of the skin, and when the rash is limited to the facial area, camouflage cosmetics can be helpful. For treatment of mild and moderate folliculitis, topical antiseptics such as hexamidine solution or topical agents with anti-inflammatory properties, such as erythromycin gel or salicylic acid lotion, seem to be beneficial. Topical steroids (0.05% betamethasone) should be avoided, except in the presence of eczema. Another topical treatment that seems to be successful is colloidal oatmeal, three times a day for 1 week [26]. Once lesions are widespread or uncomfortable to the patient, oral doxycycline (100 mg/day) for 3–6 weeks can also be used [16], and has been shown to diminish rash severity and improve quality of life [27]. Another tetracycline, minocycline, can also be helpful for the rash [28]. Finally, if the acneiform rash is severe, discontinuation of anti-EGFR therapy is recommended, and it may be resumed at lower doses after regression of lesions to grade 1.

The exact pathophysiology of this acneiform rash remains unclear. It is believed that inhibition of EGFR-mediated pathways affecting basal keratinocytes induces many crucial events of growth arrest and apoptosis, decreases cell migration, and increases cell attachment and differentiation, and inflammation [29]. With the release of chemoattractants (such as CXCLs and CCLs) and recruitment of leukocytes, inflammation is primarily responsible for the characteristic signs and symptoms associated with the rash [30]. An interesting fact is that skin toxicity seems to be related, in some circumstances, to clinical outcome and survival, and could be potentially useful as a surrogate marker for treatment efficacy and outcome [31].

Other typical skin toxicities observed include nail fragility, hair changes, and xerosis. Patients under anti-EGFR therapy can develop dry skin resembling the xerosis in atopic eczema, with scaly and itchy skin. If secondary infection by *Staphylococcus aureus* appears, a flare-up with acute oozing dermatitis and yellow crusting may also be seen. Nail toxicity appears in 10%–15% of patients, not earlier than 4–8 weeks, and is characterized by a paronychial inflammation with painful fissures in the nail folds, and the nails are more delicate and tend to grow more slowly [21]. In addition, skin fragility and easy bruising are generally observed, sometimes with mucosa involvement, such as vaginal dryness and/or aphthous ulcers of the oral or nasal mucosa.

Some hair changes can also occur. They are characterized by a trichomegaly, with the eyelashes becoming more rigid and longer and the scalp hair becoming more brittle and slow growing. Hypertrichosis with small vellus hairs may develop on the face in female patients [32].

Gastrointestinal Toxicity

Postchemotherapy diarrhea is the end result of extensive crypt damage in the small bowel and colon, resulting in an excess of fluid in the bowel lumen. The exact pathophysiology of anti-EGFR agent–related diarrhea remains unclear. EGF is involved in the maintenance of mucosal integrity and is also a potent mitogen of the gastric epithelium; it stimulates mucin production and enhances prostaglandin synthesis [33, 34].

EGF deficiency has been shown to interfere with the maturation of the squamous epithelium of the tongue, esophagus, and gastrointestinal tract without gut changes [35], with resulting diarrhea, constipation, nausea, and vomiting as side effects [36, 37]. When cetuximab is combined with irinotecan, diarrhea is present more frequently and is also more intense than that observed with irinotecan alone [38].

Diarrhea is also a dose-limiting toxicity (DLT) for most small molecule EGFR TKIs. Major mucosal toxicity has been associated with gefitinib administered at higher doses, although the mechanism of action is yet to be determined [39, 40]. Veronesse et al. [40] showed that 10 of 13 patients with colorectal cancer treated with gefitinib concomitantly with irinotecan, 5-fluorouracil (5-FU), and leucovorin showed a gastrointestinal syndrome characterized by abdominal pain and diarrhea, requiring dose reduction. In this case, the toxicity precluded the further development of this combination. As a single agent, gefitinib was given to pretreated elderly patients with NSCLC; grade 1–2 diarrhea was present in 24% of patients and grade 4 diarrhea was present in 2.5% [35].

Other Side Effects of Anti-EGFR Therapies

Interstitial lung disease (ILD) is known to be an adverse event of some cancer chemotherapeutic agents and following local radiotherapy [41]. Recently, gefitinib-related ILD emerged as a serious toxicity. In Japan, 28,000 patients diagnosed with NSCLC were treated with gefitinib between August 2002 and April 2003. ILD was diagnosed in 616 patients (2.2%), and resulted in a fatal outcome in 246 patients (0.86%), according to a report from Astra Zeneca [42]. Of note, 74% of the patients with gefitinib-related ILD had pre-existing pulmonary emphysema and 20% had idiopathic pulmonary fibrosis. The pathophysiology of gefitinib-related ILD remains unclear, but it seems that EGFR plays an important role in the maintenance and repair of epithelial tissues regulating mucin production in airways [43]. Also, it seems that gefitinib induces pulmonary side effects, mainly in patients with underlying pulmonary diseases. Therefore, Inoue et al. [44] recommend special attention with gefitinib in patients with lung comorbidities and also the careful assessment of clinical respiratory symptoms and radiographic findings in patients under gefitinib therapy, especially during the first 1–2 months of treatment.

Side Effects of Anti-HER-2 Therapies

There are two major classes of anti-HER-2 therapeutic agents: mAbs such as trastuzumab and small-molecule TKIs such as lapatinib, which is directed toward the ATP-binding domain in the intracellular portion of the receptor [1].

Trastuzumab

Trastuzumab was the first mAb approved for the treatment of HER-2–positive metastatic breast cancer (MBC), and offers an overall survival gain when combined with chemotherapy in comparison with chemotherapy alone [45]. Recently, five studies showed that adjuvant trastuzumab improves disease-free survival and, in some of them, overall survival [46–49].

Trastuzumab has been humanized from the original mAb, thereby allowing chronic administration in humans without the development of a HAMA response, which is characterized by anaphylactic or other immune reactions and rapid drug clearance [50]. Approximately 40% of patients receiving trastuzumab experience some degree of infusion-related symptoms, such as a flu-like syndrome that includes fever and chills, mainly during the first infusion. Other common reactions include tumor site pain, shortness of breath, muscle weakness, cutaneous rash, diarrhea, and headache. Trastuzumab is administered i.v. over 90 minutes for the first infusion, and with a primary line of saline solution. If the first infusion is well tolerated, subsequent doses can be administered over 30 minutes.

One major concern is the cardiac toxicity related to trastuzumab administration. In 2002, a retrospective review of seven phase II and phase III trials of trastuzumab (a total of 1,219 patients) evaluated the incidence and the characteristics of trastuzumab-associated cardiac dysfunction. Cardiac dysfunction was specifically defined as follows: cardiomyopathy characterized by a decrease in left ventricular ejection fraction (LVEF), either global or more severe in the septum; symptoms of congestive heart failure (CHF); associated signs of CHF; decline in LVEF of at least 5% to <55% with signs and symptoms of CHF; or a decline of 10% to <55% without signs or symptoms of CHF [51]. Using these criteria, 27% of patients receiving trastuzumab and doxorubicin, 13% of patients treated with trastuzumab and paclitaxel, and 3%–7% of patients undergoing therapy with trastuzumab alone developed cardiac dysfunction. Most of these patients were symptomatic (75%) and improved with standard treatment for CHF (79%). Since these results, trastuzumab combined with anthracyclines is not recommended outside clinical trials.

Adjuvant trastuzumab as used in the Herceptin® Adjuvant (HERA) trial, which enrolled more than 5,000 patients, caused severe CHF in 0.6% of women receiving trastuzumab, compared with 0% of women in the observation arm; symptomatic CHF (including severe CHF) occurred in 2% of patients in the trastuzumab arm versus 0.1% of patients in the observation arm; a confirmed significant LVEF drop occurred in 3% of women receiving trastuzumab, compared with 0.5% of women in the observation arm [42]. In the Breast Cancer International Research Group 006 trial, class 3 and 4 CHF were detected in 0.38% of patients in the doxorubicin, cyclophosphamide, and docetaxel (AC-D) arm, 1.87% of patients in the AC-D plus trastuzumab arm, and 0.37% of patients in the docetaxel, carboplatin, and trastuzumab arm [44]. In the National Surgical Adjuvant Breast and Bowel Project B-31 trial, the addition of trastuzumab to classic therapy (AC followed by paclitaxel) resulted in a higher rate of class 3–4 CHF, 4.1% versus 0.3%. Cardiac toxicity was not seen in the FinHer trial, but the number of patients in that trial was much smaller than in the other adjuvant trials [43].

Some trials combining liposomal doxorubicin with trastuzumab in MBC patients have been reported [52–55]. In the first trial, with 39 patients, only one developed an asymptomatic decrease in LVEF and another patient developed clinical CHF [51]. In another trial, with 30 patients, no symptomatic CHF occurred, but three patients experienced protocol-defined cardiotoxicity [48]. These results suggest that the combination of liposomal anthracyclines with tras-

tuzumab in HER-2–positive MBC is a good strategy to maximize efficacy without preclusive cardiotoxicity rates.

In 2005, Ewer et al. [56] showed that patients who experienced cardiotoxicity while receiving trastuzumab therapy generally recovered their cardiac function when the drug was discontinued, based on the follow-up of 38 patients diagnosed with trastuzumab-related cardiotoxicity. This improvement usually occurred in a short period of time (mean time of 1.5 months) after withdrawal of trastuzumab. In addition, the authors showed that trastuzumab-related cardiotoxicity is not associated with detectable ultrastructural abnormalities, in contrast to anthracycline-related cardiotoxicity.

The pathophysiology of trastuzumab-related cardiotoxicity has not yet been completely elucidated. During heart development, neuregulin-1, produced in the endocardium, signals in a paracrine manner to the ErbB-2–ErbB-4 receptor heterodimers present in the directly apposed myocardium. As a consequence, neuregulin–ErbB complexes are considered as playing an essential role during the morphogenetic process of the heart, and also in the regulation of excitation/contraction of the embryonic heart [57]. In the adult heart, ErbB-2 and ErbB-4 are localized to the T-tubule system of cardiomyocytes [58]. In a study of cell cultures from late embryonic or neonatal rat hearts, it was found that neuregulin-1 promoted the proliferation and survival of cardiomyocytes, and stimulated their hypertrophic growth, as assessed by the expression of atrial natriuretic factor and α actin [59]. In addition, Crone et al. [60] demonstrated the importance of HER-2 in cardiomyocytes by generating mice with deletion of HER-2 restricted to the cardiac ventricles. However, physiologic analysis revealed parameters of dilated cardiomyopathy, including chamber dilation, wall thinning, and decreased contractility. Additionally, cardiomyocytes isolated from these conditional mutants were more susceptible to anthracycline toxicity. As a consequence, such HER-2 mutant mice developed dilated cardiomyopathy, and provided an animal model for the analysis of adverse cardiac side effects caused by trastuzumab. In conclusion, HER-2 signaling in cardiomyocytes is considered crucial for the prevention of dilated cardiomyopathy.

Certain analyses indicated that accumulation of anti–HER-2 antibody in the heart differs among patients, and higher accumulation correlates with the occurrence of adverse side effects [61]. Parameters that may influence antibody accumulation in the heart include the absolute level of cardiac HER-2 protein, which can be altered in diseased hearts [62]; HER-2 protein in cardiomyocytes, which is particularly enriched in T tubules; and the diameter of the T-tubule compartment, which can also be greater in diseased hearts [63, 64]. Therefore, a greater T-tubular diameter could enhance the accessibility of the antibody trastuzumab to the cardiac HER-2 protein, explaining the higher risk for trastuzumab-related cardiotoxicity in some patients.

Lapatinib

TKIs are ATP mimetics that competitively bind to the ATP-binding cleft at the activation loop of target kinases, thereby inhibiting their kinase activity. This is the case for lapatinib, a small-molecule agent that inhibits both EGFR/ErbB-1 and HER-2/ErbB-2 TKs. This drug has shown growth arrest and apoptosis in EGFR and HER-2–dependent tumor cell lines [65]. Lapatinib is active in trastuzumab-refractory MBC patients when used alone or in combination with chemotherapy, and as first-line treatment in metastatic disease, with potential benefit in patients with brain metastases [66].

In phase I trials, lapatinib alone was well tolerated in heavily pretreated patients, with cutaneous rash, diarrhea, nausea/vomiting, fatigue, and anorexia being the most frequently observed grade 1 or 2 adverse events [67, 68]. There were no grade 4 toxicities, but grade 3 diarrhea was observed at the 900-mg twice-daily dose level. The incidence of diarrhea was linearly related to dose but not to serum concentration of the drug, suggesting that this toxicity evolves from a local effect of the drug on the gut epithelium. In the phase I study (EGF10009) that examined the safety profile of lapatinib in combination with paclitaxel, 11 (of 12) patients (92%) experienced at least one drug-related adverse event. The most frequently reported drug-related adverse events were: diarrhea (92%), vomiting (67%), rash (58%), nausea (42%), fatigue (42%), anorexia (33%), and constipation (33%) [69]. In the phase II trial testing the combination of lapatinib plus capecitabine versus capecitabine alone in 316 patients (164 versus 152), diarrhea of any grade was higher in the combinational arm (60% versus 39%), but only two women (1%) developed grade 4 diarrhea when lapatinib was administered [70].

Most recently, skin events among 1,126 patients treated with lapatinib, across eight trials, were analyzed, with dermatitis (all grades) occurring in 38% of patients, and 3% being grade 3 [71]. Regarding the potential cardiotoxicity of lapatinib, Perez et al. [72] analyzed cardiac function in 3,558 patients treated with lapatinib in 43 phase I–III clinical trials. In this cardiac safety evaluation, only 58 patients (1.6%) experienced LVEF decrease, with the incidence of symptomatic LVEF decrease being only 0.2%.

Side Effects of Antiangiogenic Therapies

Angiogenesis is critical in some physiological processes, such as organogenesis and morphogenesis during embry-

onic development, and wound healing, for example. However, abnormal growth of new blood vessels is present in pathological conditions such as diabetic retinopathy, rheumatoid arthritis, psoriasis, and tumor development and metastasis [73]. Angiogenesis is stimulated by some proteic angiogenic factors such as vascular endothelial growth factor (VEGF)/vascular permeability factor [74, 75], platelet-derived growth factor (PDGF), and basic and acidic fibroblast growth factor, among others [76, 77]. VEGF, the most important protein involved in the angiogenesis process, is an endothelial cell–specific mitogen. It promotes the growth of vascular endothelial cells derived from arteries, veins, and even lymphatics, and is essential for normal embryonic vasculogenesis. The inactivation of a single VEGF allele in mice results in embryonic lethality [78].

In 2004, the FDA approved bevacizumab (Avastin®; Genentech, Inc., South San Francisco, CA), a humanized mAb against VEGF, as the first antiangiogenic therapy to be used in combination with irinotecan and 5-FU–based chemotherapy in previously untreated metastatic colorectal cancer patients. More recently, two small molecules blocking the VEGF receptor (VEGFR) have shown promising results in the treatment of renal cell carcinoma and gastrointestinal stromal tumors (GISTs): sorafenib (Nexavar®; Bayer Pharmaceuticals Corporation, West Haven, CT), approved by the FDA in 2005 as a second-line treatment for advanced renal cell carcinoma after cytokine failure, and sunitinib (Sutent®; Pfizer, Inc., New York), approved in 2006 for patients with GIST previously treated with imatinib and for advanced renal cell carcinoma as a first-line treatment. Both agents are considered multitarget kinase inhibitors, in addition to their role as VEGFR-2 inhibitors, and are described in another section. Side effects of the main antiangiogenesis inhibitors are detailed in Table 3.

Bevacizumab

In a randomized phase II study evaluating the efficacy and safety of bevacizumab in combination with 5-FU plus leucovorin in patients with previously untreated advanced colorectal cancer [79], venous thromboembolism was the most significant adverse event, together with hypertension, proteinuria, and epistaxis. Forty patients, of the 67 (59%) who received bevacizumab in combination with chemotherapy, experienced bleeding episodes, in comparison with only four patients (11%) in the chemotherapy alone arm. Furthermore, 13 patients (19%) experienced thrombotic episodes, in comparison with 9% in the control arm [80].

It is well recognized that the incidence of venous thromboembolic events and a hypercoagulable state in gastrointestinal malignancies is in the range of 10%–15% [81]. Kilickap et al. [80] suggested that antagonizing VEGF, the major endothelial mitogen, leads to a decrease in the renewal capacity of endothelial cells in response to trauma, which in turn causes endothelial dysfunction and defects in the interior vascular lining, exposing subendothelial collagen. VEGF antagonism could also cause decreased matrix deposition in the supporting layers of vessels [82]. Therefore, the final picture of anti-VEGF therapy might consist of not only a tendency to bleed, as a result of a decreased renewal capacity of endothelial cells, but also an increased frequency of thrombotic events, as a result of tissue factor activation secondary to the exposure of the subendothelial collagen.

Kabbinavar [83] showed, in a substudy of nine patients receiving bevacizumab in the previously mentioned phase II colorectal study, that bevacizumab therapy did not result in changes in coagulation assays (prothrombin time and activated partial thromboplastin time), markers of fibrinolysis (euglobulin clot lysis time, antiplasmin-2, *d*-dimer), or platelet function. Treatment with bevacizumab and chemotherapy did result in elevated levels of factor VIII or von Willebrand factor. In discordance with bevacizumab data, a clinical trial of the VEGFR antagonist SU5416 in combination with gemcitabine and cisplatin in NSCLC patients [84] showed that SU5416 treatment induced a significant elevation in markers of vascular activation (von Willebrand factor, soluble e-selectin, and soluble tissue factor) and markers of increased potential for coagulation (soluble tissue factor and endogenous thrombin potential).

Bevacizumab combined with irinotecan, 5-FU, and leucovorin (IFL) produces a higher risk for hypertension and epistaxis. Grade 3 hypertension was noted in 11% of patients in the combination arm versus 2.3% of patients in the IFL arm. The median time to onset of the hypertension was 131 days (range, 7–316 days), and it was managed successfully with oral antihypertensive agents. In 2% of patients, there were wound-healing problems and gastrointestinal perforations [85]. Furthermore, in the phase III trial of the paclitaxel–carboplatin combination versus paclitaxel, carboplatin, and bevacizumab as first-line treatment in 878 patients with advanced nonsquamous NSCLC, fatal lung bleeding was observed in 1.2% of the patients [86]. Tumors located near to great vessels, cavitated, and presenting squamous cell features were at major risk for this serious complication.

The pathophysiology of hypertension related to anti-VEGF therapies seems to be related to depressed angiogenesis at the microcirculation level, as reflected by reduced microvessel density [87]. This reduction is a normal com-

Table 3. Different side effects of antiangiogenesis inhibitors

Side effect	Bevacizumab	Sorafenib	Sunitinib
Hypertension	+	+	+
Proteinuria	+	−	+
Thrombotic event	+	+	+
Bleeding	+	+	+
Gastrointestinal perforation	+	+	+
Wound healing	+	+	+
Fatigue	+	+	+
Mucositis	−	+	+
Diarrhea	−	+	+
Skin	−	Facial erythema, splinter subungual hemorrhage, ± alopecia	Hair depigmentation, splinter subungual hemorrhage, ± periorbital edema
Hand–foot reaction	−	+	+
Myelosuppression	−	+	+

From Perez-Soler R, Chachoua A, Hammond LA et al. Determinants of tumor response and survival with erlotinib in patients with non-small cell lung cancer. J Clin Oncol 2004;22:3238–3247, and Foon KA, Yang XD, Weiner LM et al. Preclinical and clinical evaluations of ABX-EGF, a fully human anti-epidermal growth factor receptor antibody. Int J Radiat Oncol Biol Phys 2004;58:984–990.

ponent of the aging process that has been demonstrated to occur to a greater degree in hypertensive adults [88]. The resultant diminution of vascular surface area leads to greater peripheral vascular resistance [89]. Nevertheless, it is unclear whether diminished microvessel density is the cause or the result of hypertension [90]. It is interesting to observe that VEGF exerts some of its angiogenic effects by enhancing the transcription and activity of endothelial nitric oxide synthase [91]. VEGF can rapidly induce a hypotensive response even before angiogenesis has occurred. Indeed, impressive reductions in blood pressure were demonstrated with intracoronary and i.v. infusions of VEGF [92]. Therefore, therapies directed against VEGF are prone to cause hypertensive status, sometimes resembling pre-eclampsia [90].

Finally, two cases of reversible posterior leukoencephalopathy syndrome (RPLS), characterized by headache, seizures, impaired vision, acute hypertension, and typical magnetic resonance imaging findings in T2, showing diffuse hyperintensity selectively involving the parieto-occipital white matter, were associated with bevacizumab treatment [93–95] (Fig. 2). RPLS is a brain-capillary leak syndrome related to hypertension, fluid retention, and the cytotoxic effects of immunosuppressive agents on the vascular endothelium. It seems that severe hypertensive encephalopathy leads to RPLS and vasogenic edema of the posterior cerebral white matter, induced by endothelial dysfunction and a disrupted blood–brain barrier. It is speculated that bevacizumab may induce vasospasm, which in association with hypertension in these patients led to RPLS. Accordingly, VEGF inhibitors must be used with caution in patients with poorly controlled hypertension, preferentially after adequate blood pressure control [91].

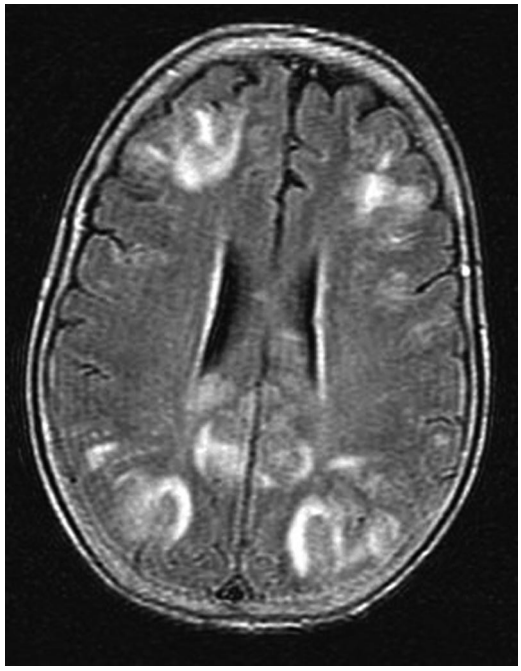

Figure 2. Reversible posterior leukoencephalopathy syndrome and bevacizumab. From Glusker P, Reckt L, Lane B. Reversible posterior leukoencephalopathy syndrome and bevacizumab. N Engl J Med; 2006:354:980–982, with permission.

Multitargeted Kinase Inhibitors

Sorafenib is an inhibitor of c-Raf and b-Raf kinases [96] and also a potent inhibitor of VEGFR-2, VEGFR-3, Flt-3, c-Kit, and the PDGF receptor (PDGFR) [97]. Sorafenib showed encouraging results as a single agent in renal cell carcinoma, and because of its inhibitory effect of b-Raf, a serine-threonine kinase activated in melanoma and papillary thyroid cancers, it has been investigated in these cancers.

The results of a large phase II, multicenter, randomized discontinuation trial published by Ratain et al. [98] revealed significant clinical antitumor activity of sorafenib in patients with renal cell carcinoma, with a favorable toxicity profile. For the 202 patients treated, the most notable adverse events were fatigue (73%), rash (66%), hand–foot reaction (62%), diarrhea (58%), hypertension (43%), and dyspnea (38%). The most common grade 3 or 4 adverse event was hypertension, which was observed in 31% of patients. Antihypertensive therapy with a variety of agents was initiated in 46% of patients. One isolated case of RPLS was reported [99].

More recently, Escudier et al. [100] reported that treatment with sorafenib in advanced clear-cell renal cell carcinoma, while able to prolong progression-free survival (hazard ratio, 0.44; 95% confidence interval, 0.35–0.55; $p < .01$), was associated with similar greater toxic effects, notably, diarrhea, rash, fatigue, hand–foot syndrome, alopecia, and nausea.

A very common skin toxicity of sorafenib (and also of sunitinib, which is described later) is the hand–foot skin reaction, or acral erythema, characterized by painful symmetrical erythematous and edematous areas on the palms and soles, commonly accompanied by paraesthesias. Sometimes the lateral sides of the fingers or the periungual zones can be affected. Hyperkeratosis and desquamation commonly occur. This hand–foot skin reaction was one of the DLTs found in the phase I program with sorafenib, in three of seven patients receiving 600 mg twice daily [101]. The actual dose of sorafenib commonly administered is 400 mg twice daily. The pathogenesis of acral erythema is still unknown, but the dose dependence in most cases suggests a direct toxic effect of the causative agent. Sunitinib and sorafenib both inhibit VEGFR and Flt-3, but neither of these receptors is known to be expressed in keratinocytes. Histological examination of epidermal changes suggests maturation modifications, such as swelling of epidermal cells in the superficial stratum spinosum, the presence of dyskeratotic keratinocytes, which suggests apoptotic cells, and superficial bullous lesions [102]. The dermis contains nonspecific modifications that suggest inflammation.

Other skin toxicities of the multitargeted kinase inhibitors include rash, stomatitis, alopecia, pruritus, and subungual splinter hemorrhages [102]. These hemorrhages are characterized by straight black or red lines under the nails. It seems that they originate from thrombotic or embolic mechanisms. Initially thought to be a typical sign of bacterial endocarditis, they were subsequently reported to be also present in different settings, such as antiphospholipid syndrome, severe rheumatoid arthritis, thromboangeitis obliterans, mitral stenosis, at high altitude, or when arterial catheters are used [103–105]. VEGFRs could be involved constitutively in the continuous renewal of the delicate spiral capillaries that sustain frequent microinjuries at finger extremities. Blockade of these receptors might prevent the physiological repair of traumatized nail-bed capillaries and facilitate the emergence of subungual splinter hemorrhages. The idea that nail beds could offer a simple way to monitor the antiangiogenic effects of drugs that target VEGFR should be assessed in prospective studies. A facial and scalp rash is commonly seen after 1–2 weeks of treatment and appears as an erythematous and squamous rash, very similar to classic moderate seborrheic dermatitis [96].

Another multitargeted therapy currently used in renal cell cancer and GIST is sunitinib, a mixed-action antiangiogenic agent with both direct antiproliferative effects in tumor cells and antiangiogenic properties, targeting VEGFRs, PDGFR-β, and c-Kit [106]. In a phase I trial, the DLTs reported were reversible grade 3 fatigue, grade 3 hypertension, and grade 2 bullous skin toxicity. The recommended dose was 50 mg/day, and sore mouth, edema, and thrombocytopenia were the main adverse events [107]. In a phase II study, including 106 patients, of second-line therapy of advanced renal cell cancer, the most common adverse events were fatigue in 30 patients (28%) and diarrhea in 21 patients (20%). Importantly, neutropenia was found in 45 patients (42%), elevation of lipase in 30 patients (28%), and anemia in 27 patients (26%) [108]. During the phase III study including 312 patients with advanced GISTs, fatigue was the most common adverse event (34%). Serious treatment-related hypertension was reported in 3% of sunitinib-treated patients. Of note, 4% (8 patients) of the patients treated with sunitinib developed hypothyroidism [109]. Thyroid function was prospectively evaluated in 42 GIST patients treated with sunitinib through serial measurements of thyroid-stimulating hormone (TSH), during a median follow-up of 37 weeks (range, 10–167 weeks). TSH concentration changes were documented in 26 of 42 patients (62%): 15 (36%) developed persistent, primary hypothyroidism, four (10%) developed isolated TSH suppression, and seven (17%) experienced transient, mild TSH elevation. The risk for hypothyroidism increased with the duration of sunitinib therapy. Six of 15 (40%) patients with

hypothyroidism had suppressed TSH concentrations before developing hypothyroidism, suggesting thyroiditis. The authors concluded that the observations of TSH suppression in some patients and a subsequent absence of visualized thyroid tissue by ultrasonography in other patients suggest that sunitinib may induce destructive thyroiditis through follicular cell apoptosis [110].

Another adverse event of sunitinib with particular importance is hair depigmentation, which generally appears after 5–6 weeks of treatment, but it is reversible as early as 2–3 weeks after treatment discontinuation [111]. Sunitinib-induced hair depigmentation is thought to be caused by a blockade of stem cell factor or suppression of c-Kit signaling [112].

Conclusions

In the so-called targeted therapy era, important improvements in disease-free and overall survival have been reported. This is particularly true in the case of trastuzumab, which is responsible for halving the risk for relapse in patients with primary early breast cancer whose tumors overexpress HER-2. This magnitude of benefit has not been seen since the development of tamoxifen, which binds the estrogen receptor, in the 1970s.

Undoubtedly, targeted therapies are very important drugs in the treatment of different cancers, alone or in combination with classic cytotoxic agents. This class of drugs inhibits specific targets in tumor cells or in the tumor microenvironment, explaining their generally favorable toxicity profile, with limited effects on bone marrow and intestinal epithelium.

However, it is important to analyze the biologic effects of targeted therapy in cancer cells as well as in normal tissues. Many of the adverse events related to these agents have been described only after more prolonged use, such as the case of cardiac toxicity due to trastuzumab or ILD reported with gefitinib. Some of these effects were unpredictable and not observed during the early phases of drug development. In fact, very few of the side effects can be linked to the mechanism of action of the drugs themselves.

A more comprehensive analysis of the underlying mechanisms of these toxicities can give us new insights into how to better select the optimal patient candidates for these therapies. In particular, it would be interesting to determine whether the skin toxicity of anti-EGFR agents could be used as surrogate marker of treatment response, and whether the hypothyroid effects of sunitinib could eventually be therapeutic against thyroid cancer.

Oncology has emerged from the empirical era, where systemic therapy was administered to all patients irrespective of particular tumor features, to the targeted therapy era, with treatment individualization. With these advances in systemic therapy, clinical practice has certainly changed in many countries. However, because of their accompanying high costs, they have also deepened the separation between wealthy and underprivileged countries and people. Careful understanding of the underlying biology and accurate patient selection will help us to avoid unnecessary costs and potentially allow these new drugs to be available for the majority of patients who need them, leading to better quality and quantity of life.

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