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Review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biologic therapies: an infectious diseases perspective—cell surface receptors and associated signaling pathways

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ABSTRACT

Background: The present review is part of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) consensus document on the safety of targeted and biologic therapies.
Aims: To review, from an infectious diseases perspective, the safety profile of therapies targeting cell surface receptors and associated signaling pathways among cancer patients and to suggest preventive recommendations.
Sources: Computer-based Medline searches with MeSH terms pertaining to each agent or therapeutic family.
Content: Vascular endothelial growth factor (VEGF)-targeted agents (bevacizumab and aflibercept) are associated with a meaningful increase in the risk of infection, likely due to drug-induced neutropaenia, although no clear benefit is expected from the universal use of anti-infective prophylaxis. VEGF tyrosine kinase inhibitors (i.e. sorafenib or sunitinib) do not seem to significantly affect host's susceptibility to infection, and universal anti-infective prophylaxis is not recommended either. Anti–epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab or panitumumab) induce neutropaenia and secondary skin and soft tissue infection in cases of severe papulopustular rash. Systemic antibiotics (doxycycline or minocycline) should be administered to prevent the latter complication, whereas no recommendation can be established on the benefit from antiviral, antifungal or anti-*Pneumocystis* prophylaxis. A lower risk of infection is reported for anti-ErbB2/HER2 monoclonal antibodies (trastuzumab and pertuzumab) and ErbB receptor tyrosine kinase inhibitors (including dual-EGFR/ErbB2 inhibitors such as lapatinib or neratinib) compared to conventional chemotherapy, presumably as a result of the decreased occurrence of drug-induced neutropaenia.
Implications: With the exception of VEGF-targeted agents, the overall risk of infection associated with the reviewed therapies seems to be low. **J. Aguilar-Company, Clin Microbiol Infect 2018;▪:1**

Introduction

This review is part of a larger effort launched by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Study Group for Infections in Compromised Hosts (ESGICH) and is

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aimed at analysing, from an infectious diseases perspective, the safety profile of biologic and targeted therapies. By means of a set of unrestricted computer-based Medline searches based on the MeSH terms appropriate for each agent or therapeutic family, we identified literature pertaining to the subject. In addition, package information and boxed warning alerts from regulatory agencies (European Medicines Agency (EMA) and US Food and Drug Administration (FDA)) were reviewed. Methodologic details are provided in the introductory section of the present Supplement [1]. For each agent or class of agents, a common outline is offered, as follows: (a) summary of mechanism of action, approved indications and most common off-label uses; (b) theoretically expected impact on the host's susceptibility to infection; (c) available evidence emerging from the clinical use of that agent (i.e. randomized clinical trials (RCTs), postmarketing studies, case series and single case reports); and (d) suggested preventive and risk minimization strategies.

Here we specifically focus on the risk of infection entailed by the use of antineoplastic agents targeting different cell surface receptors and associated intracellular signaling pathways (Table 1).

Vascular endothelial growth factor–targeted agents: bevacizumab and aflibercept

Mechanism of action, approved indications and off-label use

Angiogenesis, the formation of new capillary blood vessels from the preexisting vasculature, constitutes a key process in tumour progression by mediating invasion and metastasis of cancer cells [2]. A complex network of multiple proangiogenic signaling molecules, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF) or placental growth factor (PlGF) families, as well as their respective receptors, stimulate intracellular signaling pathways that trigger formation of new blood vessels, rapid tumour growth and metastatic spread. Of these molecules, VEGF-A represents a dominant angiogenesis promoter that stimulates the endothelial cell proliferation and migration, ultimately leading to the formation of new blood vessels [3]. Accordingly, increased VEGF mRNA expression has been demonstrated in many human tumours, including lung [4], breast [5], gastrointestinal tract [6], renal cell [7] and ovarian [8] carcinomas. In addition, a high level of intratumoural and circulating expression of VEGF-A has been found to be significantly related with poor survival [9,10]. VEGF-A acts via two tyrosine kinase receptors: VEGFR-1 (also known as Flt-1 (*fms*-like tyrosine kinase)) and VEGFR-2 (also known as KDR (kinase-insert domain containing receptor)), which are present on the surface of endothelial cells. However, VEGF-B and PlGF bind only to VEGFR-1. Not surprisingly, inhibition of VEGF family members (VEGF-A to VEGF-D) and their corresponding receptors and downstream signaling pathways has become an attractive therapeutic target, demonstrating improved outcomes across several tumour types (Fig. 1).

Bevacizumab (Avastin, Roche), the first antiangiogenic drug to be approved in 2004 as an antitumoural agent, is a humanized IgG1 monoclonal antibody that targets VEGF-A and prevents binding to VEGFR-1 and VEGFR-2 on the surface of endothelial cells [11]. Bevacizumab has been approved by the EMA in combination with fluoropyrimidine-based therapy for the treatment of metastatic colorectal cancer [12–14], in combination with paclitaxel or capecitabine for metastatic breast cancer [15,16], and in combination with platinum-based chemotherapy for non–small cell lung cancer (NSCLC) other than predominantly squamous cell histology [17,18] or with erlotinib in the presence of an activating mutation in the *EGFR* gene [19]. Further indications include advanced and/or metastatic renal cell carcinoma (RCC) in combination with interferon (IFN)-α-2a [20], epithelial ovarian, fallopian tube or primary

Table 1
Summary of infection risks associated with use of agents targeting cell surface receptors and associated signaling pathways, and suggested recommendations

Agents	Targeted molecule or pathway	Currently approved indications	Increased risk of infection	Observations and recommendations
Bevacizumab, panitumumab, aflibercept	VEGF-A/B, PlGF	CRC, breast cancer, NSCLC, RCC, ovarian cancer, fallopian tube cancer, primary peritoneal cancer, cervical cancer	Major	• Increase in risk of infection (likely due to drug-induced neutropaenia) • Increased risk of gastrointestinal perforation (with secondary peritonitis and bacteraemia), particularly in patients with CRC, previous diverticulitis, radiotherapy or recent surgical or endoscopic procedures • No expected benefit from universal use of anti-infective prophylaxis (individualized risk assessment)
Ramucirumab, sorafenib, sunitinib, axitinib, pazopanib, regorafenib vandetanib, cabozantinib	VEGFR-2, tyrosine kinase domain of VEGFR and other angiogenic pathways	CRC, gastric cancer, NSCLC, RCC, HCC, GIST, pancreatic neuroendocrine tumour, thyroid cancer, soft tissue sarcoma	None/major	• No apparent increase in risk of infection with VEGF tyrosine kinase inhibitors • Increase in risk of infection with ramucirumab (similar to VEGF-targeted agents, although clinical experience is more limited)
Cetuximab, panitumumab	EGFR/HER1	*RAS* wild-type CRC, HNSCC	Major	• Increase in risk of infection (mainly due to drug-induced neutropaenia and superinfection of papulopustular rash) • No expected benefit from universal use of antiviral, antifungal or anti-*Pneumocystis* prophylaxis • Prevention of papulopustular rash (low-potency topical steroids, moisturizer and sunscreen for first 6 weeks; doxycycline or minocycline for first 6–8 weeks)
Trastuzumab, trastuzumab emtansine, pertuzumab	ErbB2/HER2	HER2-positive breast cancer, HER2-positive gastric cancer	None	• No apparent increase in risk of infection (lower incidence of neutropaenia compared to conventional chemotherapy)
Erlotinib, gefitinib, afatinib, neratinib, lapatinib, osimertinib	Tyrosine kinase domains of EGFR/HER1, ErbB2/HER2 and other ErbB family members	NSCLC, pancreatic cancer	None	• No apparent increase in risk of infection (lower incidence of neutropaenia compared to conventional chemotherapy)

CRC, colorectal carcinoma; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumour; HCC, hepatocellular carcinoma; HER, human epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; NSCLC, non–small cell lung cancer; PDGF, platelet-derived growth factor; PlGF, placental growth factor; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

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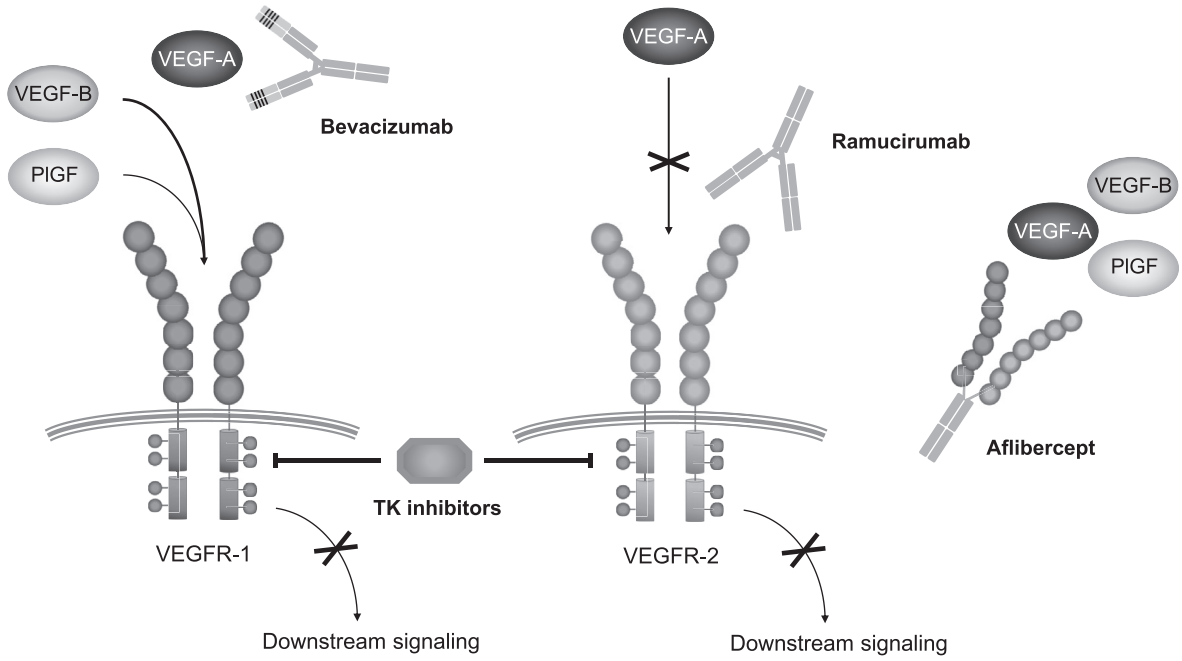

Fig. 1. Structure and mode of action of VEGF/VEGFR-targeted agents. Bevacizumab is a humanized IgG1 monoclonal antibody targeting VEGF-A (the most biologically active of the VEGF family members). Ramucirumab is a humanized IgG1 monoclonal antibody targeting VEGFR-2, therefore impeding the binding of VEGF-A (VEGF-B and PlGF bind only to VEGFR-1). Aflibercept is a fusion protein composed of the ligand-binding domains of VEGFR-1 and -2 linked to the Fc portion of IgG1. Small molecules (sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib and cabozantinib) block the downstream signaling cascade by means of the inhibition of the tyrosine kinase (TK) activity of the intracellular domain of VEGFR, either alone or in combination with other angiogenic pathways (multikinase inhibitors). VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

peritoneal carcinoma in combination with platinum-based chemotherapy [21–23] and recurrent or metastatic cervical carcinoma in combination with different chemotherapy regimens [24]. The recommended dose as an intravenous (iv) infusion varies from 5 to 15 mg/kg every 2 to 3 weeks, depending on the tumour type.

Aflibercept (Zaltrap, Sanofi-Aventis) is a recombinant fusion protein composed of the ligand-binding domains of the extracellular portions of VEGFR-1 and VEGFR-2 linked to the fragment crystallizable (Fc) portion of human IgG1, which acts as a soluble decoy receptor, inhibiting the binding of VEGF-A, VEGF-B and PlGF to VEGFR [25]. On the basis of the improvement in overall survival observed in combination with folinic acid, 5-fluorouracil and irinotecan (FOLFIRI) after progression on an oxaliplatin-containing regimen, aflibercept is currently approved in combination with FOLFIRI for patients with metastatic colorectal cancer [26]. Aflibercept is administered at an iv dose of 4 mg/kg every 2 weeks.

Expected impact on susceptibility to infection

Neutropaenia occurs during therapy with bevacizumab and aflibercept. The blockade of the biologic functions of VEGF can delay leukocyte recovery after concomitant conventional cytotoxic chemotherapy, thereby increasing the incidence and severity of resulting neutropaenia [27]. Bevacizumab may modulate intracellular T cell immunity within the tumour microenvironment and eventually T cell proliferation, migration and activation [28]. In addition, the occurrence of gastrointestinal perforation (potentially leading to secondary peritonitis or bacteraemia) is a well-established complication of VEGF-targeted agents, with a pooled incidence of 0.9% (and a related mortality of 21.7%) in a meta-analysis of bevacizumab trials [29]. Similar figures have been reported for aflibercept [30]. This complication is more common among patients with colorectal carcinoma and RCC, as well as in those with previous diverticulitis or peptic ulcer disease, receipt of local radiotherapy, or recent surgical or endoscopic procedures [31]. The physiologic proangiogenic role of VEGF in normal (non-tumour) tissue also explains the increased risk of delayed post-operative wound healing and postoperative complications (including surgical site infection) observed with anti-VEGF therapies, particularly among patients with colorectal carcinoma [32,33].

Available clinical data

Since its FDA approval for the treatment of metastatic colorectal carcinoma in 2004, data derived from a large number of RCTs allows to delineate the clinical impact of bevacizumab on infection susceptibility. As previously mentioned, neutropaenia constitutes a frequent complication with this agent, with incidence rates for all-grade and high-grade events of 25.0% and 18.5%, respectively, in a meta-analysis with over 15 000 patients. The risk of febrile neutropaenia was also increased compared to placebo or control arms (relative risk (RR), 1.31; 95% confidence interval (CI), 1.08–1.58) [34]. A large meta-analysis pooling data from 41 RCTs and more than 30 000 patients with various cancer types (mostly colorectal carcinoma) concluded that the use of bevacizumab significantly increased the incidence of all-grade (RR, 1.45; 95% CI, 1.27–1.66) and serious (RR, 1.59; 95% CI, 1.42–1.79) infection. The pooled incidences for all-grade, severe and fatal infection were 7.8%, 3.0% and 0.9%, respectively. In subgroup analyses, the association between bevacizumab therapy and infection was modulated by the use of concomitant therapies (i.e. taxanes, capecitabine, gemcitabine or oxaliplatin) and was revealed to be evident only for patients with NSCLC, colorectal carcinoma, breast cancer and gastric cancer. Although detailed information on infectious syndromes was not available for most trials, the infection risk related to bevacizumab seemed to be limited to febrile neutropaenia, fistulae or abscesses and pneumonia, but not for sepsis or colitis [35]. Bacteraemia due to *Bacteroides fragilis* [36] and *Campylobacter* spp. [37] was reported,

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presumably due to the effect of bevacizumab on the gastrointestinal blood supply, facilitating bowel infarction and bacterial translocation. There are anecdotal reports of *Pneumocystis jiroveci* pneumonia [38,39] and necrotizing fasciitis [40]. However, the contributing role of previous or concomitant cytotoxic therapies is difficult to discern. In addition, the use of granulocyte-colony stimulating factor (G-CSF) was not consistent across study arms in most of these studies. Despite its deleterious impact on wound healing, no increased periprocedural morbidity (including infections at the insertion site) has been observed after placing long-term central venous catheters in bevacizumab-treated patients [41], although a more recent study has provided conflicting results [42].

Data from pivotal phase 2 and 3 trials also confirmed that the incidence of neutropaenia was higher with aflibercept than comparator therapy across different cancer types, such as NSCLC [43] or metastatic colorectal carcinoma [26]. A meta-analysis that included more than 4000 patients from ten RCTs of patients treated with aflibercept reported a pooled incidence of serious and fatal infection of 7.3% and 2.2%, respectively. Unfortunately, most meta-analysed studies lack data granularity on the type of infection and causative agent. The use of aflibercept was associated with an increased risk of developing serious (RR, 1.87; 95% CI, 1.52–2.30) and fatal (odds ratio, 2.16; 95% CI, 1.14–4.11) infection. The observed risk of infection was substantially higher with aflibercept than bevacizumab, a finding that could be potentially be explained by the fact that aflibercept blocks not only the action of VEGF-A but also VEGF-B and PlGF (Fig. 1). It should be kept in mind that the interpretation of these findings is complicated because of the heterogeneity across studies, with patients receiving either aflibercept-based combination therapy or aflibercept alone, and a variety of regimens (including placebo) in the control arms [44].

The development of osteonecrosis of the jaw, a complication in which the pathogenesis of oral microbiota and *Actinomyces* spp. seem to be involved [45], has been described in patients receiving bevacizumab [46] and aflibercept [47], even in the absence of prior bisphosphonate therapy or local radiotherapy.

Conclusions and suggested prevention strategies

- In view of available data, therapy with VEGF-targeted agents is associated with a meaningful increase in the risk of infection, likely due to the occurrence of drug-induced neutropaenia.
- In order to reduce the length of drug-induced neutropaenia, the use of G-CSF may be considered in cases of delayed recovery of absolute neutrophil counts.
- Clinicians caring for patients receiving such therapy should be aware of the increased risk of gastrointestinal perforation (potentially resulting in secondary peritonitis and bacteraemia), particularly in the presence of predisposing conditions such as colorectal carcinoma, previous diverticulitis or local radiotherapy, or recent surgical or endoscopic procedures.
- No clear benefit is expected from the universal use of anti-infective prophylaxis for patients receiving VEGF-targeted agents, although an individualized infection risk assessment seems advisable.

VEGF tyrosine-kinase receptor–targeted agents: sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib, cabozantinib and ramucirumab

Mechanism of action, approved indications and off-label use

Various agents targeting vascular endothelial growth factor receptor (VEGFR)—or specifically its tyrosine kinase domain (as well as those of other angiogenic signaling pathways)—have been developed in an attempt to improve antitumour efficacy and overcome resistance to VEGF blockade alone [48].

Sorafenib (Nexavar, Bayer), sunitinib (Sutent, Pfizer), axitinib (Inlyta, Pfizer) and pazopanib (Votrient, Novartis Pharmaceuticals) are small-molecule tyrosine kinase inhibitors that target the VEGF pathway, either alone (axitinib) or in combination with a number of other pathways such as PDGF, c-Kit, B-type Raf kinase (BRAF) or *fms*-like tyrosine kinase-3 (FLT3) (the so-called multikinase inhibitors). Sorafenib was approved in 2007 as a first-line agent for patients with advanced hepatocellular carcinoma (HCC) and relatively preserved liver function [49]. Since then, further approved indications include advanced RCC and progressive, locally advanced or metastatic differentiated (papillary, follicular or Hürthle cell) thyroid carcinoma refractory to radioactive iodine. Sunitinib is approved by the EMA for patients with advanced RCC, unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) after failure of imatinib therapy, and with unresectable or metastatic pancreatic neuroendocrine tumours [50]. Axitinib and pazopanib are also approved for advanced RCC after failure of prior treatment with sunitinib or IFN-α-2a [51,52]. In addition, pazopanib can be used in patients with selected subtypes of advanced soft tissue sarcoma who have received prior chemotherapy for metastatic disease or whose disease has progressed within 12 months after neoadjuvant therapy [53].

More recently, the EMA have approved regorafenib (Stivarga, Bayer) for the treatment of HCC, GIST and metastatic colorectal carcinoma in patients with progression to previous therapies (including other VEGF/VEGFR-targeted agents such as sorafenib or sunitinib) [54,55], and vandetanib (Caprelsa, AstraZeneca) and cabozantinib (Cabometyx (tablets) or Cometriq (capsules), Ipsen Pharma) for advanced RCC and unresectable or metastatic medullary thyroid carcinoma [56,57]. These drugs have potent receptor tyrosine kinase inhibitory activity targeted no only against VEGFR but also against rearranged during transfection receptor and angiopoietin 1 receptor.

All these small-molecule tyrosine kinase inhibitors are orally administered at various doses.

Ramucirumab (Cyramza, Eli Lilly) is a fully humanized IgG1 monoclonal antibody that binds to the extracellular domain of VEGFR2 with high affinity, thus blocking the binding of VEGF-A (and other VEGF family members different than VEGF-B). This agent has shown to significantly improve survival outcomes when administered in association with paclitaxel for advanced gastric or gastro-oesophageal junction cancer (or as a single agent for patients unable to receive taxane derivatives) [58], with FOLFIRI for metastatic colorectal cancer after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine [59], and with docetaxel as second-line therapy for NSCLC [60]. Ramucirumab is provided as an iv infusion (8–10 mg/kg) every 2 to 3 weeks.

Expected impact on susceptibility to infection

As previously suggested for VEGF-targeted agents, the blockade of VEGF signaling pathway through the inhibition of the tyrosine kinase receptor activity seems to modulate T cell functionality within the tumour microenvironment [61]. It is unlikely that such effect exerts a negative impact on host immunity. In fact, *in vivo* studies suggest just the opposite because sorafenib enhances local natural killer (NK) cell, T cell, macrophage and dendritic cell responses in murine models of HCC [62,63]. Nevertheless, it is unclear whether these immunomodulatory properties of tyrosine kinase inhibitors may act in the same sense outside the tumour environment, as therapy with sunitinib and sorafenib has been found to inhibit activation, proliferation and cytokine production in peripheral blood T cells [64,65]. In RCC patients, sunitinib induced

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significant decreases in total leukocyte and neutrophil counts, as well as in certain peripheral blood lymphocyte subpopulations (total $CD3^+$ and $CD4^+$ subsets). These parameters returned to baseline levels when sunitinib was discontinued [66].

Available clinical data

In general terms, the safety profile of multitargeted tyrosine kinase inhibitors appears to be worse than that of agents selectively targeting the VEGF pathway. However, the most common adverse events with sorafenib and sunitinib (the multikinase inhibitors with the most long-term clinical experience) include hypertension, diarrhoea, fatigue and skin rash, but not infectious events. Stomatitis and hand–foot syndrome are other toxicities frequently observed [67]. Although the pooled incidence of all-grade neutropaenia with sorafenib therapy was reported to reach 18.0% in a meta-analysis with more than 3000 patients, high-grade events were rare (5%), and its occurrence was not influenced by the receipt of concomitant chemotherapy [68]. A significant risk of potentially life-threatening liver injury has been identified with pazopanib [69]. Likely as a result of its more selective action on the VEGFR family, the incidence of cutaneous toxicity and neutropaenia seems to be lower with axitinib than with sorafenib [70]. A meta-analysis of fatal adverse events in RCC trials with sorafenib, sunitinib and pazopanib published before 2011 identified only three episodes of fatal sepsis among more than 4000 patients [71]. Recent RCTs assessing the efficacy and safety of cabozantinib [72,73] or sorafenib [74] versus a mammalian target of rapamycin (mTOR) inhibitor for advanced RCC, or regorafenib versus placebo for HCC after failure of sorafenib [75], have not revealed a significant risk of infection. Hypertension, hand–foot syndrome and diarrhoea were again the most frequent toxicities observed in patients with unresectable or metastatic GIST receiving regorafenib [76]. Interestingly, the decreased in $CD3^+$ and $CD4^+$ T cell counts observed in RCC patients receiving sunitinib in the aforementioned study was not associated with the occurrence of opportunistic infection [66]. Overall, these results suggest that the use of tyrosine kinase inhibitors, either multitargeted or selective for the VEGF pathway, are not associated with a meaningful increase in the risk of infection.

In the pivotal phase 3 trial that demonstrated the survival benefit of ramucirumab in combination with FOLFIRI for metastatic colorectal carcinoma, the incidence of grade 3 or higher neutropaenia was higher in the ramucirumab group than in the placebo group (38.4% vs. 23.3%, respectively), although febrile episodes were rare and were distributed between both arms [59]. About 15% of patients receiving ramucirumab plus docetaxel in the pivotal phase 3 RCT for advanced NSCLC experienced febrile neutropaenia, although there were no fatal episodes [60]. Neutropaenia was also the most common grade 3 or higher adverse event among patients receiving ramucirumab (either alone or associated with paclitaxel) in pivotal trials for advanced gastric or gastro-esophageal junction adenocarcinoma [58,77]. In a phase 3 RCT comparing ramucirumab plus docetaxel versus placebo plus docetaxel for locally advanced or metastatic urothelial carcinoma, sepsis was the most common fatal adverse event and occurred in 1.6% of patients allocated to the ramucirumab arm compared to none within the placebo arm [78]. Finally, a meta-analysis of individual patient safety data from five RCTs and about 5000 patients reported pooled incidences for gastrointestinal perforation and wound-healing complications of 1.1% and 0.5%, respectively [79].

Conclusions and suggested prevention strategies

- In view of available data, therapy with VEGF tyrosine kinase inhibitors does not increase the risk of infection. Therefore, no benefit is expected from the use of anti-infective prophylaxis for patients receiving such therapy.
- It is likely that the use of anti-VEGFR2 monoclonal antibodies (ramucirumab) is associated with an increase in the risk of infection similar to that observed for VEGF-targeted agents (including the occurrence of drug-induced neutropaenia and gastrointestinal perforation as contributing factors). However, it should be noted that accumulated clinical experience is so far more limited.

Epidermal growth factor receptor–targeted agents: cetuximab and panitumumab

Mechanism of action, approved indications and off-label uses

The epidermal growth factor receptor (EGFR), also known as ErbB1 or human epidermal growth factor receptor 1 (HER1), is a transmembrane glycoprotein consisting of a cysteine-rich extracellular ligand binding domain, a hydrophobic transmembrane segment and a cytoplasmic domain with intrinsic tyrosine kinase activity. By stimulating cell growth and differentiation after binding of specific ligand, it plays a crucial role in many types of cancer. EGFR is one of the four proteins in the ErbB (or HER) family of receptor tyrosine kinases, also including ErbB2/HER2, ErbB3/HER3 and ErbB4/HER4. These receptors homo- or heterodimerize upon ligand binding, which is followed by the transautophosphorylation of the dimer partner. Then the phosphorylated proteins initiate intracellular signaling pathways. The Ras/MAPK and Ras/PI3K/Akt/mTOR pathways are major signaling networks linked to EGFR activation and to cell proliferation and survival [80].

Cetuximab (Erbitux, Merck) is a chimeric IgG1 monoclonal antibody, and panitumumab (Vectibix, Amgen) is a fully human IgG2 monoclonal antibody; both target EGFR (Fig. 2). These agents are approved for patients with *RAS* wild-type metastatic colorectal cancer, either in combination with chemotherapy as first- or second-line treatment [81–85], or as single agents after failure of oxaliplatin- and irinotecan-based regimens [86,87]. Cetuximab, in combination with radiation, has also demonstrated to improve locoregional control and overall survival in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) [88], and to increase overall survival in combination with platinum and fluorouracil chemotherapy as first-line therapy for recurrent or metastatic HNSCC [89]. The currently approved dosing regimen for cetuximab is an initial iv dose of 400 mg/m^2 body surface area, followed by weekly doses of 250 mg/m^2. Panitumumab is provided in a dosage of 6 mg/kg every 2 weeks.

Expected impact on susceptibility to infection

Clinical research suggests that EGFR-targeted monoclonal antibodies increase the risk of infection. Basic research suggests that heparin-binding epidermal growth factor (EGF)-like growth factors (HB-EGF) play an important role in regulating the proliferation of hematopoietic maturing cells. The biologic effects of HB-EGF are exerted through EGFR, as demonstrated after the blockade of its activity by anti-EGFR monoclonal antibodies [90,91]. Thus, cetuximab and panitumumab might affect the proliferation of neutrophils and lead to neutropaenia [92]. EGF is also involved in tumour necrosis factor α–induced respiratory burst and phagocytic activity through the EGFR tyrosine kinase pathway [93].

Down-regulation of EGFR-dependent signaling in nontumour tissues may also impair normal immune innate immunity function. Toll-like receptors (TLRs) constitute an important class of sensors that detect highly conserved microbial motifs (pathogen-associated molecular patterns) and activate cellular responses, resulting in the

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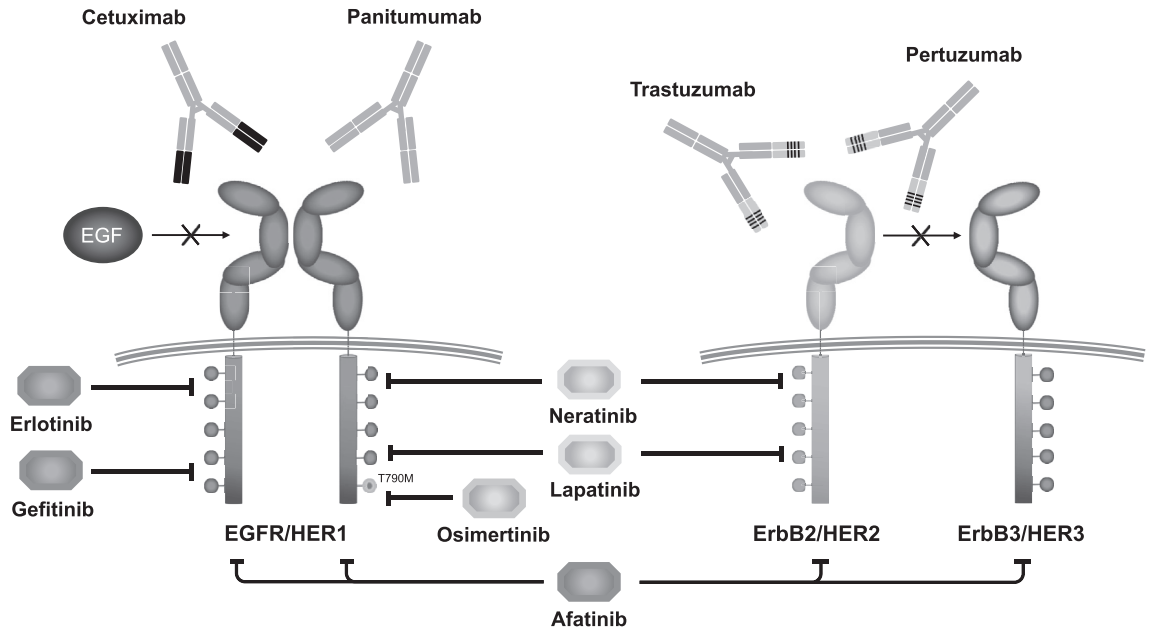

Fig. 2. Structure and mode of action of ErbB/HER family members-targeted agents. Cetuximab and panitumumab are chimeric IgG1 and fully human IgG2 monoclonal antibodies, respectively, both targeting EGFR/HER1 and blocking the binding of EGF to its receptor (which induces homo- or heterodimerization followed by transautophosphorylation and initiation of the intracellular signaling pathway). Trastuzumab and pertuzumab are humanized monoclonal antibodies binding ErbB2/HER2 at different sites, impeding heterodimerization with other ErbB family members (particularly ErbB3/HER3) and subsequent initiation of the signaling cascade. Small molecules inhibit the tyrosine kinase activity of the intracellular receptor domain. Erlotinib and gefitinib are selective for EGFR/HER1, afatinib is a pan-ErbB tyrosine kinase inhibitor, lapatinib and neratinib are dual EGFR1/ErbB2 tyrosine kinase inhibitors and osimertinib is an EGFR tyrosine kinase inhibitor active in presence of the T790M *EGFR* resistance mutation. EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor.

synthesis of antimicrobial molecules such as interferon. TLR-3 function has been found to depend on EGFR activation and Scr binding [94]. Dysregulated EGFR function in normal respiratory epithelium and dendritic cells may also contribute to the risk of infection.

Most patients treated with EGFR-targeted agents experience dermatologic toxicity, most notably in the forms of papulopustular rash, xerosis and paronychia [95]. EGFR is instrumental in maintaining epidermal homeostasis through regulation of keratinocyte proliferation, differentiation, migration and survival. Therefore, EGFR-targeted therapies (either by monoclonal antibodies or small-molecule tyrosine kinase inhibitors) lead to strong dysregulation in the keratinocyte cycle and strong inflammatory responses. Such skin toxicity, which occurs in up to 75% of patients in a dose-dependent fashion after 1 to 2 weeks of therapy, seems to be associated with EGFR blockade itself, rather than off-target inhibition of other signaling pathways. The eruption consists of folliculocentric pruritic papules that evolve into pustules with a seborrheic distribution (head, neck, trunk and proximal upper extremities), occasionally coalescing to form lakes of pus [96]. The occurrence of severe rash is more frequent with monoclonal antibodies (10–17%) than with small-molecule tyrosine kinase inhibitors (5–9%). Microorganisms do not appear to contribute to the pathogenesis of EGFR-targeted agent-induced rash in the earlier phases, as the initial pustule is sterile [97]. Nevertheless, secondary infection of the affected skin with bacteria, dermatophytes or viruses may follow [98].

Available clinical data

Two meta-analyses have evaluated the risk of high-grade infections (grade 3 or higher according to the Common Terminology Criteria for Adverse Events, with febrile neutropaenia classified as high-grade infection) associated with the use of cetuximab or panitumumab [99,100]. Both included phase 2 and 3 RCTs published before 2014. In these meta-analyses, treatment with anti-EGFR monoclonal antibodies was associated with a higher incidence of severe infection and neutropenic fever, with RRs of 1.34 (95% CI, 1.1–1.62) and 1.49 (95% CI, 1.1–1.62), respectively. Another meta-analysis from 2011 that included data from more than 7100 subjects recruited across 14 RCTs reported an overall incidence of severe neutropaenia among cetuximab-exposed patients of 33%, although it reached 61% for those with NSCLC. The RR for cetuximab-induced neutropaenia was 1.12 (95% CI, 1.05–1.19), with higher risks observed for colorectal carcinoma and NSCLC [101].

Skin and soft tissue infections complicating papulopustular rash induced by EGFR-targeted therapy have been reported in the literature as case reports and retrospective case series. Of note, some of them included complicated forms due to *Staphylococcus aureus,* such as skin abscess infections requiring surgical management [102–104] or bacteraemic infections [105,106]. Two meta-analyses of RCTs and nonrandomized intervention studies evaluating the efficacy of oral tetracyclines (doxycycline of minocycline) for the prevention of papulopustular rash showed significant benefit in terms of reduced incidence of moderate to severe forms [107,108]. Topical corticosteroids and antibiotics (e.g. clindamycin) have been also used as prophylaxis or treatment, although its efficacy has not been adequately evaluated. The use of systemic antibiotic therapy is recommended in cases of severe rash or superinfection [98].

Finally, a large meta-analysis based on 14 066 patients from 26 RCTs reported that the use of anti-EGFR monoclonal antibodies significantly increased the risk for severe (RR, 1.34; 95% CI, 1.10–1.62) but not for fatal infections (RR, 1.62; 95% CI, 0.81–3.26). Interestingly, such increased risk was limited to specific tumour types (colorectal carcinoma, NSCLC and HNSCC) and to cases in which cetuximab or panitumumab were used in conjunction with cisplatin or irinotecan. Unfortunately, detailed data on specific

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infection types or causative microorganisms were lacking, as most of these events were simply categorized as febrile neutropaenia, pneumonia or sepsis [100].

Conclusions and suggested prevention strategies

- In view of available data, therapy with EGFR-targeted monoclonal antibodies is associated with a meaningful increase in the risk of infection, mainly as a result of the occurrence of drug-induced neutropaenia and secondary infection in cases of severe papulopustular rash.
- In order to reduce the length of drug-induced neutropaenia, the use of G-CSF may be considered in cases of delayed recovery of absolute neutrophil counts.
- No clear benefit is expected from the universal use of antiviral, antifungal or anti-*Pneumocystis* prophylaxis for patients receiving such therapy, although an individualized infection risk assessment seems advisable.
- Prevention of the development of papulopustular rash in patients receiving EGFR-targeted monoclonal antibodies should be based on low-potency topical steroids (i.e. hydrocortisone 1%) combined with moisturizer and sunscreen for the first 6 weeks of therapy. On the basis of results coming from RCTs, the administration of systemic antibiotics (doxycycline 100 mg every 12 hours or minocycline 100 mg daily) for the first 6 to 8 weeks is also strongly recommend.

Human epidermal growth factor receptor 2 (ErbB2/HER2)-targeted agents: trastuzumab and pertuzumab

Mechanism of action, approved indications and off-label uses

In contrast to other members of the ErbB family, ErbB2/HER2 has no known direct activating ligand. It exists as a monomer on the cell surface and may be in a constitutively activated state or may become active upon heterodimerization with other family members such as Erb1/HER1 or ErbB3/HER3 (or even with members of different families, such as insulin-like growth factor receptor 1) [109]. ErbB2/HER2 induces cell proliferation through activation of downstream signaling cascades (i.e. Ras/PI3K/Akt/mTOR or Ras/MAPK pathways). In addition, ErbB2/HER2 dimerization promotes the rapid degradation of certain cell-cycle inhibitor proteins, leading to cell-cycle progression [110]. Overexpression of ErbB2/HER2 is present in approximately 20% to 30% of invasive breast tumours [111,112] and 7% to 34% of gastric cancers [113], and it implies poorer prognosis and shorter disease-free and overall survival [109]. Similar to the EGFR/HER1 pathway, the blockade of overexpressed ErbB2/HER2 signals may be based on monoclonal antibodies targeting the ligand-binding extracellular domain or on small molecules inhibiting the tyrosine kinase activity of the intracellular region.

Trastuzumab (Herceptin, Roche) is a humanized IgG1 monoclonal antibody that binds the extracellular domain of ErbB2/HER2, leading to decreased receptor heterodimerization, increased receptor degradation and (likely) immune activation [114]. When administered as adjuvant therapy, trastuzumab has significantly improved long-term outcomes in patients with HER2-positive early or metastatic breast cancer, as well as in combination with neoadjuvant chemotherapy for locally advanced disease [115]. Trastuzumab is also EMA approved in combination with a fluoropyrimidine-based regimen as fist-line therapy for HER2-positive metastatic gastric or gastro-oesophageal junction adenocarcinoma. The recommended dose is 6 mg/kg at once every three weeks. Trastuzumab emtansine (Kadcyla, Roche), an antibody–drug conjugate that results from the covalent linking of trastuzumab to the microtubule inhibitor DM1 (a maytansine derivative), has recently been approved. Upon binding to ErbB2/HER2, trastuzumab emtansine undergoes receptor-mediated internalization and subsequent lysosomal degradation, leading to the intracellular release of DM1-containing cytotoxic catabolites.

Pertuzumab (Perjeta, Roche) is a humanized monoclonal antibody targeted at a different epitope of the extracellular domain of Erb2/HER2 than trastuzumab (subdomain II instead of subdomain iv) that also prevents heterodimerization with other HER members (in particular with ErbB3/HER3, which results in the most potent activating heterodimer of the Ras/PI3K/Akt/mTOR pathway) (Fig. 2). The combination of pertuzumab and trastuzumab provides more effective dual inhibition of ErbB2/HER2 [116] and better clinical outcomes [117] than either agent alone. Therefore, pertuzumab has been approved by the EMA in combination with trastuzumab and docetaxel for HER2-positive metastatic or unresectable breast cancer, and as neoadjuvant treatment for locally advanced, inflammatory or early stage breast cancer at high risk of recurrence.

Expected impact on susceptibility to infection

It is currently unclear how monoclonal antibodies targeting ErbB2/HER2 modulate the immune system, although *in vitro* studies suggest that such therapy may in fact activate both innate and adaptive responses, particularly those mediated by NK cells [118–120]. In addition, since the FDA granted approval for trastuzumab in 2006, long-term accumulated clinical experience does not indicate that these targeted agents increase the risk of infectious complications.

Available clinical data

A 2015 meta-analysis of 10 094 patients from 13 RCTs showed that treatment with trastuzumab carried a modest but statistically significant increase in the risk of high-grade infection (RR, 1.2; 95% CI, 1.07–1.37) and febrile neutropaenia (RR, 1.28; 95% CI, 1.08–1.52). However, such association was mainly driven by studies in which trastuzumab was used in combination with conventional chemotherapy and not as single agent. In addition, the incidence of high-grade neutropaenia was not significantly higher with trastuzumab than with the comparator. The authors concluded that the underlying mechanism remains unclear [121]. A recent study demonstrated that patients with chronic hepatitis B virus or hepatitis C virus infection receiving trastuzumab and chemotherapy had no higher incidence of liver toxicity than the control group. In addition, no patients developed hepatitis B virus or hepatitis C virus reactivation [122].

Conclusions and suggested prevention strategies

- In view of available data, therapy with ErbB2/HER2-targeted monoclonal antibodies might be associated with a minor increase in the risk of infection, although the biologic rationale and clinical evidence supporting this association are poor.
- No benefit is expected from the use of anti-infective prophylaxis for patients receiving such therapy.

ErbB receptor tyrosine kinase–targeted agents: erlotinib, gefitinib, afatinib, osimertinib, lapatinib and neratinib

Mechanism of action, approved indications and off-label uses

The mechanisms by which the EGFR signaling pathway becomes oncogenic are numerous and are often specific for each type of

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cancer. In NSCLC, mutations in the intracellular tyrosine kinase domain of EGFR enhance ligand-inducing autophosphorylation and confer increased sensitivity to specific tyrosine kinase inhibitors [123–126]. The discovery of these activating mutations in the tyrosine kinase domain of the *EGFR* gene has represented a major step forward in the design of personalized therapeutic approaches in patients with NSCLC. The most common oncogenic mutations are deletions in exon 19 (present in 45–50% of cases) and a point mutation (L858R) in exon 21 (35–45% of cases). The estimated frequency of *EGFR* mutations is approximately 15% and is more prevalent in certain subgroups, such as women, patients with an Asian background, never-smokers and those with adenocarcinoma histology [127].

First-generation EGFR tyrosine kinase inhibitors include gefitinib (Iressa, AstraZeneca) [128–130] and erlotinib (Tarceva, Roche) [131,132]. Both agents act by reversible (noncovalent) binding to the tyrosine kinase domain of EGFR. As an irreversible pan-ErbB inhibitor, afatinib (Giotrif, Boehringer Ingelheim) [133,134] is a second-generation tyrosine kinase inhibitor that binds to all members of the ErbB family (including ErbB2/HER2) (Fig. 2). These three agents have been shown to confer remarkable improvements in response rates and progression-free survival compared to conventional chemotherapy across several RCTs. Thus, gefitinib, erlotinib and afatinib have been approved by the FDA and EMA as first-line therapies for the treatment of patients with advanced NSCLC harbouring *EGFR*-sensitizing mutations. Both agencies have approved the use of afatinib for patients with metastatic squamous NSCLC who have experienced disease progression despite treatment with a platinum-based chemotherapy [135]. Erlotinib is also approved for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen [136]. Finally, erlotinib has also been EMA approved in combination with gemcitabine for the treatment of metastatic pancreatic cancer [137].

Unfortunately, the acquisition of resistance mutations in the *EGFR* gene to first- and second-generation tyrosine kinase inhibitors is a common phenomenon, prompting the development of more potent targeted agents [138]. The *EGFR* T790M mutation has been identified as the most common acquired resistance mechanism [139]. This newer generation of tyrosine kinase inhibitors includes lapatinib (Tyverb, Novartis Pharmaceuticals) [140], neratinib (Nerlynx, Puma Biotechnology) [141] and osimertinib (Tagrisso, AstraZeneca) (Fig. 2). Lapatinib is a selective dual-EGFR/ErbB2 reversible inhibitor that has been approved, in combination with capecitabine, trastuzumab or an aromatase inhibitor, for advanced HER2-positive breast cancer. Neratinib is a dual EGFR/ErbB2 irreversible inhibitor that has received FDA approval for the treatment of early-stage HER2-positive breast cancer after receipt of adjuvant trastuzumab-based therapy. Finally, osimertinib is a potent, irreversible third-generation EGFR tyrosine kinase inhibitor active for both sensitising and T790M *EGFR* resistance mutations. Osimertinib shows central nervous system penetration, with cases reported of sustained tumour regression in brain metastases. The FDA and EMA have approved its use for patients with locally advanced or metastatic NSCLC harbouring the T790M mutation.

Expected impact on infection risk

ErbB receptor tyrosine kinase inhibitors exhibit an acceptable safety profile, with most adverse events consisting of rash, diarrhoea, hepatotoxicity and, less frequently, interstitial lung disease and pneumonitis [142–144]. The occurrence of infection during therapy seems to be rare because the EGFR pathway is not directly involved in the regulation of immune system. Nevertheless, some evidence suggests that the EGFR pathway is responsible for specific protective responses in the airway epithelium, leading to mucin production and secretion (for mucociliary clearance of invading organisms), neutrophil recruitment (via interleukin 8, a potent neutrophil chemotactic chemokine) and epithelial wound healing. In theory, such findings might translate into a higher rate of respiratory tract infections among patients receiving EGFR tyrosine kinase inhibitors due to an impairment in the airway innate immunity [145].

Available clinical data

In the pivotal phase 3 trial for first-line therapy in patients with NSCLC associated with activating *EGFR* mutations, the rate of grade 3/4 neutropaenia was 0 in the erlotinib group, compared to 22% in the chemotherapy-based therapy group, whereas the occurrence of pneumonitis was similar across both arms [131]. In a second phase 3 RCT comparing erlotinib to conventional chemotherapy in patients of Asian background with *EGFR*-mutated advanced NSCLC, the overall rates of infection were 17% and 10% in the erlotinib and in the gemcitabine plus carboplatin arms, respectively, although the incidence of serious (grade 3/4) infection was considerably lower (1% for erlotinib and 0 for conventional chemotherapy). As expected, the decrease in the absolute neutrophil count was significantly more frequent among patients receiving chemotherapy than those treated with erlotinib (with rates of grade 3/4 neutropaenia of 42% vs. 0, respectively) [132]. In a pivotal RCT comparing erlotinib versus placebo as second- or third-line therapy for advanced NSCLC, infection was reported in 24% (4% for grade 3 or higher events) of patients receiving erlotinib compared to 15% (2% for grade 3 or higher events) of those receiving placebo. Episodes of serious infections, with or without neutropaenia, included pneumonia, sepsis and cellulitis. In this study, conjunctivitis was reported in 12% of patients receiving erlotinib compared to 2% of patients allocated to the placebo arm [136].

Gefitinib has been extensively evaluated in an elevated number of phase 3 trials, mostly comparing this agent with conventional chemotherapy in *EGFR*-mutated NSCLC. The pivotal IPASS trial, conducted in previously untreated Asian patients, confirmed the progression-free survival benefit of EGFR tyrosine kinase inhibitors compared to conventional chemotherapy, changing the existing paradigm of first-line therapy in advanced *EGFR*-mutated NSCLC. The rates of neutropaenia of grade 3 or higher were 3.7% in the gefitinib arm versus 67.1% in the chemotherapy arm [128]. In a meta-analysis of four RCTs including approximately 2000 patients with NSCLC, participants receiving conventional chemotherapy as first-line therapy experienced significantly higher rates of myelosuppression than those receiving gefitinib. As example, the occurrence of all-grade and grade 3 or higher neutropaenia was much less common in the gefitinib arms (7% vs. 84% and 3% vs. 69%, respectively). Across different studies, the odds ratio for grade 3 or higher neutropaenia for gefitinib (vs. chemotherapy) was 0.01. On the other hand, rash and diarrhoea were more common among gefitinib-treated patients. Although almost 70% of patients in the gefitinib arms experienced any-grade rash, the incidence of severe forms was much lower (3%) [146].

As an irreversible pan-ErbB blocker, afatinib is supposed to exert the most potent inhibitory activity and to pose a higher rate of adverse events. However, similar rates of infection (compared to placebo) have been reported for afatinib than for other EGFR tyrosine kinase inhibitors, suggesting that even a potent inhibition of EGFR/HER1 or ErbB2/HER2 does not increase infection susceptibility. Afatinib has a well-defined safety profile, with rash or acne, diarrhoea, paronychia and stomatitis or mucositis as the most common attributable adverse events. In the two pivotal phase 3 RCTs comparing afatinib versus conventional chemotherapy based

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on platinum plus pemetrexed [133] or gemcitabine plus cisplatin [134], neutropaenia and leucopenia were the most common chemotherapy-related adverse events. In the LUX-Lung 3 trial, the rates of all-grade and severe neutropaenia were 0.9% and 0.4% for afatinib compared to 31.5% and 18% for chemotherapy arm. There were three cases (1%) of interstitial lung disease among patients allocated to the afatinib arm, and four deaths in this group were deemed to be potentially treatment related by the investigator (two respiratory decompensations, one sepsis and one unknown). Cystitis was reported in 13% of patients receiving afatinib compared to 5% of those receiving chemotherapy [133]. In a phase 2b RCT comparing afatinib versus gefitinib, the frequency and severity of all-cause adverse events were similar across both study groups. Of note, 2 afatinib-related deaths were due to infectious complications (pneumonia), whereas one patient in the gefitinib group died of lung infection. The rate of grade 1/2 neutropaenia for both arms was 1%, and grade 3 cutaneous bacterial infection was observed in 1% of patients receiving afatinib [147].

In a phase 2 trial with osimertinib for relapsed NSCLC harbouring the T790M *EGFR* mutation receiving osimertinib, the most commonly observed treatment-related toxicities consisted of diarrhoea, rash, paronychia and dry skin. No infections were described, and just one patient required drug discontinuation due to the decrease in neutrophil count [148]. A phase 3 RCT comparing osimertinib versus conventional chemotherapy reported rates of all-grade neutropaenia of 8% and 23%, respectively. In addition, 10% of patients treated with osimertinib experienced nasopharyngitis compared to 5% of those receiving chemotherapy [149].

Taken together, data emerging from these pivotal RCTs suggest that the inhibition of the tyrosine kinase receptor activity linked to the ErbB family seems to be safe in terms of infectious complications and not to imply a clinically relevant impact on the host's immune response. The majority of adverse events described were limited to the development of rash, diarrhoea, mucositis and paronychia. Low rates of severe neutropaenia or infection (such as pneumonia or cutaneous infection) have been described.

Conclusions and suggested prevention strategies

- In view of available data, therapy with ErbB receptor tyrosine kinase inhibitors (including either selective EGFR/HER1 and/or ErbB2/HER2 inhibitors or pan-ErbB inhibitors) is not associated with a significant increase in the risk of infection, likely due to the lower occurrence of drug-induced neutropaenia compared to conventional chemotherapy.
- No benefit is expected from the use of anti-infective prophylaxis for patients receiving such therapy.

Transparency declaration

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