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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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