Clinical Microbiology and Infection 24 (2018) S53–S70

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Narrative review

ESCMID Study Group for Infections in Compromised Hosts (ESGICH) Consensus Document on the safety of targeted and biological therapies: an infectious diseases perspective (Intracellular signaling pathways: tyrosine kinase and mTOR inhibitors)

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ARTICLE INFO

Article history:
Received 10 November 2017
Received in revised form
8 February 2018
Accepted 11 February 2018
Available online 16 February 2018

Editor: L. Leibovici

Keywords:
BCR-ABL kinase inhibitors
Ibrutinib
Idelalisib
Infection
Janus kinase inhibitors
mTOR inhibitors
Small-molecule inhibitors

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 different intracellular signaling pathways and to suggest preventive recommendations.
Sources: Computer-based Medline searches with MeSH terms pertaining to each agent or therapeutic family.
Content: Although BCR-ABL tyrosine kinase inhibitors modestly increase the overall risk of infection, dasatinib has been associated with cytomegalovirus and hepatitis B virus reactivation. BRAF/MEK kinase inhibitors do not significantly affect infection susceptibility. The effect of Bruton tyrosine kinase inhibitors (ibrutinib) among patients with B-cell malignancies is difficult to distinguish from that of previous immunosuppression. However, cases of *Pneumocystis jirovecii* pneumonia (PCP), invasive fungal infection and progressive multifocal leukoencephalopathy have been occasionally reported. Because phosphatidylinositol-3-kinase inhibitors (idelalisib) may predispose to opportunistic infections, anti-*Pneumocystis* prophylaxis and prevention strategies for cytomegalovirus are recommended. No increased rates of infection have been observed with venetoclax (antiapoptotic protein Bcl-2 inhibitor). Therapy with Janus kinase inhibitors markedly increases the incidence of infection. Pretreatment screening for chronic hepatitis B virus and latent tuberculosis infection must be performed, and anti-*Pneumocystis* prophylaxis should be considered for patients with additional risk factors. Cancer patients receiving mTOR inhibitors face an increased incidence of overall infection, especially those with additional risk factors (prior therapies or delayed wound healing).

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https://doi.org/10.1016/j.cmi.2018.02.009

Implications: Specific preventive approaches are warranted in view of the increased risk of infection associated with some of the reviewed agents. **M. Reinwald, Clin Microbiol Infect 2018;24:S53**

Introduction

The present 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 aims to analyse, 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. Methodobiologic details are provided in the Introduction section of the present Supplement issue [1]. For each agent or class of agents, a common outline is offered: (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. This section is devoted to review the risk of infection entailed by the use of antineoplastic agents targeting tyrosine kinases and other key signaling proteins. It should be noted that the impact of antiangiogenic agents (such as monoclonal antibodies against vascular endothelial growth factor (VEGF) and its receptor, or VEGF tyrosine kinase inhibitors), antibodies against the epidermal growth factor receptor and inhibitors of the intracellular tyrosine kinase domain of cell-surface receptors of the ErbB family (including the so-called multikinase inhibitors) has been covered in another section of the issue [2].

Table 1 summarizes the development status, approved indications and theoretical impact on infectious susceptibility of the reviewed agents, whereas the suggested strategies to prevent such complications are depicted in Table 2. It should be emphasized, however, that in view of the limited data available so far for many of these agents, the provided recommendations are necessarily open for constant modifications on the basis of ongoing and future clinical observations. Increased awareness by clinicians is required to identify emerging infections occurring in patients treated with tyrosine kinase inhibitors, to report them promptly and to collect information systematically within multicentre collaborative groups in order not to miss uncommon but relevant events.

BCR-ABL tyrosine kinase inhibitors: imatinib, dasatinib, nilotinib, bosutinib and ponatinib

Mechanism of action, approved indications and off-label uses

Chronic myeloid leukaemia (CML) is characterized by the (9; 22) (q34; q11) translocation (cytogenetically visible as the Philadelphia chromosome (Ph)), which gives rise to the breakpoint cluster region gene—Abelson murine leukaemia viral oncogene homologue 1 (BCR-ABL) fusion protein, a constitutively active tyrosine kinase (TK) that induces cell survival and proliferation. Imatinib (Glivec or Gleevec, Novartis Pharmaceuticals) was approved in 2001 as the first TK inhibitor for the treatment of Ph^+ CML. Imatinib binds to the adenosine triphosphate (ATP)-binding pocket of the BCR-ABL protein, thus preventing the kinase to become active. This agent also blocks other TKs, such as the KIT (c-Kit) receptor, the stem-cell factor receptor, the discoidin domain receptors (DDR1 and DDR2) or the platelet-derived growth factor (PDGF) receptors (PDGFR-α and -β) [3,4]. Imatinib is currently approved as first-line therapy for newly diagnosed Ph^+ CML in adults and children whose disease is not suitable for haematopoietic stem-cell transplantation (HSCT), or for those with disease in blast, accelerated or chronic phases after failure of interferon (IFN)-α therapy. In addition, it is approved for relapsed or refractory Ph^+ acute lymphoblastic leukaemia (ALL), myelodysplastic or myeloproliferative diseases associated with *PDGFR* gene rearrangements, aggressive systemic mastocytosis without the D816V c-Kit mutation or with mutational status unknown, hypereosinophilic syndrome and/or chronic eosinophilic leukaemia, and unresectable, recurrent and/or metastatic dermatofibrosarcoma protuberans. Imatinib is the only first-line targeted therapy approved for patients with c-Kit–positive gastrointestinal stromal tumours, both as adjuvant therapy after resection and in the advanced/metastatic setting [3,4].

Dasatinib (Sprycel, Bristol-Myers Squibb) is a second-generation multitargeted TK inhibitor that binds to the active and inactive forms of the BCR-ABL kinase (as opposed to imatinib, which only binds to the inactive state). It has been shown *in vitro* to exert a 300-fold more potent inhibition than imatinib, being effective against most imatinib-resistant BCR-ABL mutations. Dasatinib also targets the SRC family kinases, c-Kit, PDGFR-α and -β, DDR1 and ephrin receptors. This TK inhibitor is currently approved for newly diagnosed Ph^+ CML in chronic phase, as well as for patients with Ph^+ CML in any phase or Ph^+ ALL and resistance or intolerance to prior therapy, including imatinib [3,4].

Nilotinib (Tasigna, Novartis Pharmaceuticals) was 20 to 30 times more potent than imatinib in preclinical studies. Nilotinib inhibits most imatinib-resistant BCR-ABL mutations, as well as c-Kit, PDGFR, DDR1, VEGF and ephrin receptors. It is recommended as first-line treatment of newly diagnosed Ph^+ CML in chronic phase and for patients with disease in chronic or accelerated phases resistant to or intolerant to prior therapy, including imatinib [3,4].

Bosutinib (Bosulif, Pfizer) is other dual-specific inhibitor of the SRC and ABL kinase families that remains active against most BCR-ABL resistance mutations, although it has minimal activity against PDGFR and c-Kit. More potent than imatinib, bosutinib has been approved for CML in patients who have developed resistance or intolerance to previous therapies [3].

Ponatinib (Iclusig, Incyte Corporation) is a third-generation multitargeted TK inhibitor that exhibits a unique carbon-carbon triple bond allowing BCR-ABL kinase inhibition even in presence of the T315I mutation, which alters the topology of the ATP-binding region [3]. It is approved for patients with Ph^+ ALL or CML (in all phases of disease) disease resistant or intolerant to prior TK inhibitor-based therapies.

Expected impact on infection risk

Myelotoxicity is one of the most important adverse effects associated with TK inhibitors, particularly among patients with