Risk of Infectious Complications in Hemato-Oncological Patients Treated with Kinase Inhibitors

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ABSTRACT: Infectious complications are a major cause of morbidity and mortality in patients with hemato-oncological diseases. Although disease-related immunosuppression represents one factor, aggressive treatment regimens, such as chemotherapy, stem cell transplantation, or antibody treatment, account for a large proportion of infectious side effects. With the advent of targeted therapies affecting specific kinases in malignant diseases, the outcome of patients has further improved. Nonetheless, dependent on the specific pathway targeted or off-target activity of the kinase inhibitor, therapy-associated infectious complications may occur. We review the most common and approved kinase inhibitors targeting a variety of hemato-oncological malignancies for their immunosuppressive potential and evaluate their risk of infectious side effects based on preclinical evidence and clinical data in order to raise awareness of the potential risks involved.

KEYWORDS: TKI, kinase inhibitors, infections, infectious complications, targeted therapy, EGFR, BCR-ABL, BRAF, VEGF, BCR signaling, mTOR, JAK

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Introduction

Over the last decade, the introduction of novel, innovative targeted therapies in hemato-oncological diseases has made a significant impact on the current therapeutic strategies and is associated with an outstanding clinical benefit for hematological diseases such as chronic myeloid leukemia (CML),[1] myelofibrosis (MF), and polycythemia vera (PV),[2] with additional improvement in solid tumors such as renal cell cancer,[3] lung cancer,[4] and melanoma.[5] Besides antibody therapy targeting specific epitopes, the mainstay of targeted therapies is the inhibition of specific tyrosine or serine/threonine kinases that have been implicated in disease pathogenesis and prognosis for a variety of diseases. Thus, kinase inhibitors (KIs) have undoubtedly become one of the major advances in the treatment of malignant diseases in recent years.

Yet, unpredictable and unexpected adverse effects have been reported with the use of targeted therapies, with several of these effects being recognized after long-term clinical use such as reversible posterior leukoencephalopathy by anti-vascular endothelial growth factor (VEGF) agents[6] or osteonecrosis of the jaw, which is associated with bisphosphonate treatment.

As several of these targeted agents affect critical components of the immune system, they are associated with infectious complications with potentially life-threatening consequences. This is of importance as infections in cancer patients represent a typical, often therapy-associated complication,[7] and it has been noted that for several hematologic malignancies, infections are the major contributor to nonrelapse mortality.[8]

Therefore, in this review, we give an overview on the infectious complications of different tyrosine kinase inhibitor (TKI) classes affecting different hemato-oncological diseases based on preclinical and clinical evidence. We review KIs such as epidermal growth factor receptor (EGFR) inhibitors (eg, erlotinib), multikinase inhibitors such as sorafenib, the fusion gene resulting from a fusion of the breakpoint cluster region-gene and the Abelson murine leukemia viral oncogene homolog (BCR-ABL) inhibitors (eg, imatinib), inhibitors of mammalian target of rapamycin (mTOR), inhibitors of the Janus kinase (JAK), BRAF inhibitors such as vemurafenib, and most recently, inhibitors of the B-cell receptor (BCR) signaling pathway such as ibrutinib and idelalisib. The focus of this review is on the infections associated with these classes of drugs in order to raise awareness of these complications in the treating physician. The specific KI, its mode of action and associated frequency of infectious complications are summarized in table 1 while typical infections associated with this KI and possible prophylactic measures are summarized in Table 2.

Inhibitors of BCR-ABL Tyrosine Kinase

Based on the results from the pivotal International Randomized Study of Interferon and STI571 (IRIS) trial in 2002, imatinib, as the first approved inhibitor of BCR-ABL tyrosine kinase, heralded the age of KI therapy and revolutionized the treatment of CML[9] and later on also gastrointestinal stromal tumors (GISTs) due to its additional activity in targeting c-Kit.[10] BCR-ABL, a fusion protein that results from the translocation (9;22) is the major hallmark that drives the malignant phenotype of CML, its inhibition suppressing the growth advantage of the transformed cells and potentially inducing even molecular remissions. In addition, for the subgroup of patients with acute lymphoblastic leukemia (ALL) and 9;22 translocation, inhibition of BCR-ABL added to conventional chemotherapy is the standard of care. The spectrum of KIs inhibiting BCR-ABL has grown with dasatinib, nilotinib, bosutinib, and most recently, ponatinib, further broadening the therapeutic armamentarium with the capacity of targeting mutations conferring resistance to imatinib.[11–14] However, all BCR-ABL-targeting KIs also potentially affect other targets such as SRC-family kinases as well as c-Kit, platelet-derived growth factor receptor (PDGFR)-a and -b, and ephrin receptor kinase[11], thus carrying the potential for infectious complications.

Besides inducing neutropenia and therefore increasing the likelihood of infections, preclinical studies have shown that imatinib also inhibits CD4+ and CD8+ T-cell proliferation.[15,16] In addition, the inhibitory effect on T-cell activity and proliferation has also been demonstrated for nilotinib[17] and dasatinib.[18] Furthermore, differential immunosuppressive effects between these KIs have been observed probably due to individual off-target kinase activity of these different agents.[19,20] Besides its effect on T cells, recent data have shown that TKIs impair B-cell immune responses in CML through off-target inhibition of kinases important for B-cell signaling.[21] Taken together, there is evidence of a potential immunosuppressive effect of TKIs affecting BCR-ABL, most likely due to their off-target activity.

There are suggestions that the observed immunosuppressive effect translates into an increased risk of infections clinically; nonetheless, specific data on these complications are rare in the literature: data from the initial clinical trials showed a rate of 15% upper respiratory infections in patients treated with imatinib compared to 8% in those treated with interferon/cytarabine; however, the rate of grade 3/4 reactions was similar.[9] Reactivations of hepatitis B under imatinib treatment have been repeatedly reported,[22–26] and one trial evaluated varicella zoster virus (VZV) infections,[27] occurring in only 2% of CML patients treated with imatinib. Similarly, another group found a low infection rate for CML patients under imatinib treatment.[28] For nilotinib, data from the initial trials are rather scarce; infections of any kind are not listed as nonhematological adverse effects in the Evaluating Nilotinib Efficacy and Safety in clinical Trials (ENEST trial)[29] and its three-year follow-up.[30] A retrospective multicenter analysis of imatinib-resistant or imatinib-intolerant CML patients who had been treated with nilotinib revealed infections occurring in 9% of patients, yet only 1% of them represented grade 3/4 infections.[31] Similar to imatinib, there is one case of hepatitis B reactivation in a nilotinib-treated patient.[32]

Dasatinib has been reported to show the highest off-target activity of KIs targeting BCR-ABL, and *in vitro* data hint at the strongest immunosuppressive effect for this TKI.[20] In the clinical trials, infections of any grade occurred in 27 (11%) of dasatinib-treated patients and 18 (7%) imatinib-treated patients. In the dasatinib arm, five patients died due to infection, whereas one patient died in the imatinib arm; however, the investigators deemed these infections not drug related.[33] Interestingly, the majority of infections did not occur in neutropenia. In a safety analysis of two major clinical trials for dasatinib evaluating 1150 patients for infectious complications, serious infections were rare and only one grade 3–4 opportunistic infection was observed for dasatinib.[34] In contrast to imatinib and nilotinib, however there seems to be a potential impact of dasatinib on infectious side effects: In a retrospective review of CML and ALL patients treated with dasatinib, three or more cycles of dasatinib significantly increased the risk of infection with predominantly bacterial infections,[35] and even opportunistic infections such as *Pneumocystis jirovecii* have been recently described.[36] The majority of infections occurred during neutropenia, thus confounding the effects. In another publication for patients with Ph+-ALL, the infection rate was 18% for all-grade infections and 8% for grade 3/4 infections.[37] In addition, reactivation of latent viral infections such as cytomegalovirus (CMV)[38] and even hepatitis B reactivation has been described.

For the newest TKIs targeting BCR-ABL bosutinib and ponatinib, data on infectious complications can only be derived by evaluating available safety data from the initial clinical trials. In the randomized comparison of imatinib and bosutinib (Bosutinib Efficacy and Safety in Newly Diagnosed Chronic Myeloid Leukemia [BELA] trial), the rate of upper respiratory infections has been reported to be 12% for bosutinib and 8% for imatinib, yet all these consisted of grade 1/2 infections.[39] For ponatinib, the rate of febrile neutropenia has been reported to be 1–6%, depending on the type of disease, with the highest rates observed for ALL, probably based on intensive neutropenia.[40]

Taken together, there is some, albeit minor, evidence of a slightly increased rate of infections in BCR-ABL-positive patients treated with TKIs, probably reflecting not inhibition of BCR-ABL itself but off-target kinase inhibition involved in immune system function. The broader the spectrum of the TKI, the higher the potential for immunosuppressive side effects, thus showing a differential effect, with dasatinib having the highest potential for infectious complications.

Table 1. Assessment of clinical evidence of risk of infections and corresponding references.

KINASE INHIBITOR TREATMENT REGIMEN	PATHWAY	UNDERLYING MALIGNANCY	SIGNIFICANT EVIDENCE OF KI-ASSOCIATED INFECTIOUS COMPLICATIONS[¥]	ALL GRADE INFECTIONS/ GRADE 3/4 INFECTION IN CLINICAL TRIALS [%]	REFERENCE(S)[€]
Imatinib	BCR-ABL, c-KIT	CML	Minor	15/0,2	[9]
		GIST	None	11/0	[167]
		Ph+-ALL	Minor	N/A. /38–52 (combined w. chemotherapy)	[168] [169]
Dasatinib	BCR-ABL, c-KIT	CML	Minor	10.5/ 2	[33]
		Ph+-ALL	Minor	18/8	[37]
Nilotinib	BCR-ABL	CML	None	9/1	[31]
		Ph+-ALL	None	N/A.	N/A.
Bosutinib	BCR-ABL	CML	None	12/0	[39]
Ponatinib	BCR-ABL	CML	None	6/6	[40]
		Ph+-ALL	None	6/6	[40]
Erlotinib	EGFR	NSCLC	None	5/1	[53]
Gefitinib	EGFR	NSCLC	None	N/A./3	[54]
Afatinib	EGFR	NSCLC	None	0/0	[42]
Crizotinib	ALK-4-EML	NSCLC	None	32/0	[47]
		ALK-pos. NHL	None	N/A/0	[48]
Ceritinib	ALK4-EML	NSCLC	None	N/A./0	[57]
Vemurafenib	BRAF	Melanoma	None	0/0*	[64]
Dabrafenib	BRAF	Melanoma	None	0/0*	[170]
Trametinib[§]	MEK	Melanoma	None	0/0*	[60]
Temsirolimus	mTOR	MCL	Major	25/7	[102]
		RCC	Major	27/5	[103]
Everolimus	mTOR	RCC	Major	37/13	[105]
		pNET	Major	N/A./5	[171]
		TB	Major	22/14	[172]
		Hs BRCA[$]	Major	9–15/N/A.	[110]
Sunitinib	Multikinase	RCC	None	0/0*	[173]
		pNET	None	0/0*	[174]
		GIST	None	0/0*	[175]
Sorafenib	Multikinase	RCC	None	0/0*	[128]
		HCC	None	0/0*	[176]
		FLT3-pos. AML[¥]	Moderate	N/A./55	[130]
Regorafenib	Multikinase	CRC	None	10/1	[132]
		GIST	None	0/0*	[133]
Pazopanib	Multikinase	STS	None	0/0*	[177]
		RCC	None	0/0*	[138]
Axitinib	Multikinase	RCC	None	0/0*	[178]
Ruxolitinib	JAK2	MF	Major	50/N/A.	[179]
		PV	Major	42/4	[73]
Tofacitinib	JAK3	RA	Major	23/5	[180]
Ibrutinib	BTK	CLL	Major	33/12	[157]
		MCL	Major	23/6	[145]
Idelalisib	PIK3delta	CLL[#]	Major	28/19	[164]
		NHL	Major	25/7	[146]

Notes: Kinase inhibitors are shown according to target/indication. [¥]Graded to none, minor, moderate, and major. *Infectious complications were not mentioned in the safety data or the supplements. [§]In combination with dabrafenib. [#]In combination with rituximab. [€]If possible randomized trial. [¥]Combined with chemotherapy. [$]In combination with exemestan.

Abbreviations: CML, chronic myeloid leukemia; GIST, gastrointestinal stromal tumor; Ph+-ALL, Philadelphia-chromosome-positive acute lymphoblastic leukemia; NSCLC, non-small cell lung cancer; ALK-pos. NHL, ALK-positive non-Hodgkin's lymphoma; MCL, mantle cell lymphoma; RCC, renal cell cancer; pNET, pancreatic neuroendocrine tumor; TB, subependymal giant cell astrocytoma associated with tuberous sclerosis; Hs BRCA, hormone-sensitive breast cancer; HCC, hepatocellular carcinoma; AML, acute myeloid leukemia; CRC, colorectal carcinoma; STS, soft-tissue sarcoma; MF, myelofibrosis; PV, polycythemia vera; RA, rheumatoid arthritis; CLL, chronic lymphocytic leukemia.

Inhibitors of EGFR-Activating Mutations and ALK-4-EML Rearrangement

In non-small-cell lung cancer (NSCLC), activating mutations of the EGFR and rearrangement of anaplastic lymphoma kinase (ALK) have been identified as drivers of cancer progression and initiation and inhibition of these pathways in mutated disease have been associated with significant improvement in patients' outcome (reviewed by Minuti et al.[4]). The first available TKIs for metastatic NSCLC were gefitinib and erlotinib targeting EGFR, and EGFR overexpression has been observed in lung cancer and was associated with impaired survival.[41] Recently, with afatinib, a second-generation EGFR KI has been introduced in the clinical treatment routine and has shown promising activity against the EGFR T790 mutation, which confers resistance to erlotinib and gefitinib,[42] but it is also active in first-line treatment.[43,44]

Besides targeting EGFR, it was discovered that a characteristic gene rearrangement involving the ALK gene, including its intracellular tyrosine kinase domain, can be observed in 3–6% of NSCLC patients, with the most frequent rearrangement partner being the echinoderm microtubule-associated protein-like 4 (EML4) gene.[45] The resulting kinase activity can be successfully inhibited by the TKI crizotinib. Initially developed for the treatment of ALK-positive anaplastic large cell lymphoma, crizotinib has shown significant activity with prolonged survival not only in second-line therapy[46] but also most recently in first-line therapy in NSCLC,[47] and in small series, it has shown promising activity in relapsed ALK-positive non-Hodgkin's lymphoma.[48] A second TKI targeting ALK-positive NSCLC, ceritinib, has recently been approved for AL4-EML4-rearranged NSCLC patients intolerant or resistant to crizotinib.[49]

From a clinician's point of view, EGFR-TKIs have a rather mild side-effect profile usually consisting of hepatotoxicity, rash, diarrhea, and interstitial lung disease, with supposedly ethnical differences in incidence[50]; infections seem to be a rather rare event as the EGFR pathway is not involved in immunoprocessing. However, preclinically, it has been discovered that airway epithelial surface signaling mediated by EGFR is one way of activating innate immune responses to a variety of infectious and noninfectious stimuli in the respiratory system,[51] which in theory might translate into a higher rate of respiratory infections in patients receiving EGFR-TKI therapy. Yet, when analyzing the data from the randomized trials comparing erlotinib with chemotherapy, the rate of febrile neutropenia was 0% in contrast to the chemotherapy-based therapy arm where the rate of pneumonitis was similar.[52] Data from the maintenance trial for erlotinib show a rate of grade 3/4 infections of 1% vs. 0% in the placebo arm.[53]

In the NCIC CTG BR19 trial, which tests gefitinib after surgical resection of the tumor in an adjuvant setting, Common Toxicity Criteria (CTC) grade 3/4 infections are reported in 3% of the patients and 1% of placebo-treated patients[54] and in the trials for gefitinib maintenance again tested vs. placebo infectious complications are not mentioned.[55] Afatinib, which is an irreversible Erb blocker and has supposedly the highest activity, although reported to have a higher rate of adverse events in general, shows similar rates of infectious side effects as other EGFR-TKIs[56] even when compared to placebo. Infectious side effects did not seem to be frequent with afatinib treatment,[42] suggesting that even potent inhibition of EGFR or Erb does not increase the rate of infectious side effects.

Taken together, the data from the trials suggest that EGFR-TKI treatment seems safe in terms of infectious complications and does not have clinically relevant immunosuppressive properties.

For ALK-rearranged NSCLC and its primary TKI crizotinib, data on potential immunosuppressive properties are even more scarce: in the initial trial comparing crizotinib to chemotherapy, a higher rate of grade 1/2 upper respiratory infections compared to chemotherapy was observed but grade 3/4 infections were only present in the chemotherapy arm,[46] a finding that was later also seen in the first-line trial.[47] For ceritinib, available data concerning this topic are also lacking. The only clinical trial published does not describe infections as typically occurring Adverse Events (AEs)[57]; however, the limited data surely forbid drawing a definite conclusion. Interestingly, both drugs differ in their off-target activity as crizotinib targets c-met, whereas insulin-like growth factor 1 receptor (IGF-1R) and insulin receptor (InsR) are additionally inhibited by ceritinib. Both TKIs affect the proto-oncogene 1 receptor kinase (ROS1) at clinically relevant concentrations.

In summary, the inhibition of EGFR via TKI treatment has little potential detrimental immunosuppressive effects and does not seem to increase the risk of infections. For ALK-rearranged malignancies, the (limited) data also suggest a rare occurrence of infectious complications. Nonetheless, based on the limited number of patients who have yet been exposed to crizotinib or ceretinib, the final conclusion concerning this matter can probably not be drawn at this moment.

Inhibitors of BRAF/MEK

Activating mutations of BRAF, which induce constitutive activation of the MAPK signaling pathway, have been implicated in induction and in maintaining the malignant phenotype in a variety of cancers. Vemurafenib and dabrafenib, both inhibiting BRAF, have been approved for the treatment of melanoma and have also been successfully used in other BRAF-mutated cancer entities[58,59]; yet most patients suffer a relapse later in the course of their disease. More recently, the introduction of MEK-inhibitor trametinib combined with dabrafenib has led to further increase in overall survival in melanoma patients,[60] underlining the potential of inhibition of the MAPK pathways by TKI therapy.

As the MAPK pathway has been implicated in immune system functions, especially in the processing of pattern recognition receptors such as toll-like receptors,[61] pharmacological

inhibition might, at least in theory, cause immunosuppressive properties of these drugs. Clinical data on potential infectious complications in patients treated with BRAF or MEK inhibitors are however scarce. It has been recently shown that melanoma patients treated with vemurafenib had a significant decrease in lymphocyte count, especially the CD4+ T-cell population and significantly reduced secretion of interferon-γ and interleukin 9; the effect was not observed for dabrafenib.[62] An extended analysis could find infections in 9/102 patients, especially if the patients had been additionally treated with steroids.[63] However, neither in the pivotal trial comparing vemurafenib with dacarbazin in melanoma patients[64,65] nor in the combination trials of vemurafenib with MEK inhibitors cometinib[66] or trametinib,[60] a significant rate of infectious side effects is mentioned in the safety data.

In summary, from the available data, a strong clinical evidence of severe immunosuppression with consecutive increased risk of infection cannot yet be demonstrated, although a heightened awareness should be applied if patients receive concomitant steroids.

Inhibitors of JAK

The family of JAK consists of four kinases – JAK1, JAK2, JAK3, and TYK – and plays a major role in hematopoiesis as knockout studies with JAK2-deficient mice showed an impaired development of their hematopoiesis leading to death at day 13 of gestation.[67] However, there is evidence that different JAKs induce varied transcriptional changes, typically via the signal transducer and activator of transcription (STAT) family pathway, and are involved in several diseases. The activating mutation V617F of JAK2 has been identified as one of the hallmarks in the pathogenesis of myeloproliferative neoplasms and has been detected in 95% of patients with PV and to a lesser extent in 50–60% of patients with MF and essential thrombocythemia.[68] In addition, it has also been found in a significant proportion of patients with myeloid malignancies, such as myelodysplastic syndrome, acute myeloid leukemia (AML), and CML.[69] The activation of the JAK2 V617F kinase domain causes the constitutive activation of proteins STAT5 and STAT3, which consecutively induce malignant cell transformation.[70] Interestingly, STAT3, targeted via JAK3, has also been implicated in a variety of different autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis and JAK3 inhibitors have been introduced as another class of disease-modifying drugs in rheumatoid arthritis (DMARD).[71]

Based on the CML success story, where TKIs dramatically affected outcome and clinical course of the disease, inhibitors of JAK were developed; these inhibitors, however, do not specifically inhibit the mutated kinase but JAKs in general. Although several other compounds are in development, the two US Food and Drug Administration (FDA)-approved inhibitors are ruxolitinib and tofactinib. Ruxolitinib targets JAK1 and JAK2, and after being initially approved for MF,[72] it has also quite recently been approved for PV.[73] In addition,

Table 2. Assessment of specific kinase inhibitors infections and prophylaxis recommendations based on available evidence.

PATHWAY TARGETED KINASE	AVAILABLE DRUGS	TYPICAL INFECTIONS REPORTED	PROPHYLAXIS RECOMMENDED*
BCR-ABL	Imatinib, Dasatinib, Nilotinib, Ponatinib, Bosutinib	HSV reactivation CMV reactivation Hepatitis Reactivation Febrile neutropenia URTI	May be considered
EGFR/ALK	Erlotinib, Gefitinib, Afatinib, Crizotenib, Ceritinib	URTI	None
BRAF/MEK	Vemurafenib, Dabrafenib, Trametinib	No specific	None
mTOR	Temsirolimus, Everolimus	VZV Reactivation HSV Reactivation Invasive Aspergillosis PcP	Aciclovir/Cotrimoxazole *should* be considered
Multikinase (esp. VEGF)	Sorafenib, Sunitinib, Regorafenib, Axitinib, Pazopanib	No specific	None
JAK	Ruxolitinib, Tofactinib	VZV Reactivation HSV Reactivation Invasive Aspergillosis PcP	Aciclovir/Cotrimoxazole *should* be considered
BCR-Pathway-Inhibitory	Ibrutinib, Idelalisib	Pneumonia, URTI	May be considered

Note: *Recommendation of anti-infective prophylaxis based on the data on frequency, type, and severity of infections in the current available literature, prone to change in the future.
Abbreviations: HSV, herpes simplex virus; CMV, cytomegalovirus; URTI, upper respiratory tract infection; PcP, *P. jirovecii* pneumonia.

tofactinib, an inhibitor of JAK1 and JAK3, has been approved for refractory RA based on a placebo-controlled trial, showing its potential as a DMARD.[74]

The indication that a drug targeting JAK does have a significant use in autoimmune diseases clearly hints at immunosuppressive properties and thus warrants further investigation. Indeed, preclinical data clearly show an influence of ruxolitinib and tofactinib on components of the immune system. It has been demonstrated that tofactinib not only suppresses cytokine production of CD4+ T lymphocytes in RA patients[75,76] but also inhibits proliferation of these cells.[77] For ruxolitinib, this profound effect has also been confirmed: Schönberg et al could clearly show a decrease in natural killer cells of patients treated with ruxolitinib, and this effect was clearly linked to an increase in infections in their study.[78] The same group also found that the drug impairs T-cell function by decreasing their potential of producing proinflammatory cytokines, and thus, Th1 and Th17 cells were reduced *in vivo* and *in vitro*.[79] Lastly, even dendritic cells' function and migration is hampered by ruxolitinib, further aggravating immune system dysfunction.[80]

Clinical trials and increased clinical exposure clearly underline the potential of infectious complications of JAK inhibitors. Indeed, for tofactinib, pooled data of all patients in the randomized trials covering approximately 4800 patients suggest a significant incidence of infection and infection-related mortality, which is however similar to what is observed in treatment with other biological agents for RA.[81] Similar to these other biological agents, frequent herpes zoster reactivation and even *Mycobacterium tuberculosis* reactivation has been recognized. Quite interesting is the efficacy and immunosuppressive property of tofactinib in inflammatory bowel disease[82] and also its potential role as an immunosuppressive agent in kidney transplantation.[83] Interestingly, in both of these trials, infections were the major problem not only compared to placebo but also compared to cyclosporine A in kidney transplanted patients. This is also supplanted by the prospective placebo-controlled trial of tofactinib in RA patients, where infections were associated with tofactinib treatment and even serious infections occurred in this treatment arm.[84] Typical infections represented herpes zoster, CMV, and even Epstein–Barr virus reactivation associated with posttransplant lymphoproliferative disease.

For ruxolitinib, clinical data also indicate an increased risk of infection: in the recent trials for PV, ruxolitinib treatment was associated with an increased rate of infection (42% vs. 37%) underscored by the increase in herpes zoster reactivation (6% vs. 0%).[73] In addition, in a recent phase 2 trial for patients with AML relapse treated with ruxolitinib, the most frequent grade 3 or 4 nonhematologic event was infection (most frequently, pneumonia; 15 of 26; 58%).[85] Furthermore, reports about severe opportunistic infections have been published for patients under ruxolitinib treatment, such as *Cryptococcus neoformans* pneumonia,[86] hepatitis B reactivation,[87] toxoplasmosis chorioretinitis,[88] disseminated tuberculosis,[89] and even JC virus-associated progressive multifocal encephalopathy.[90] On the other hand, recent data on its potential in treating steroid-refractory graft-versus-host disease (GvHD) clearly emphasize the immunosuppressive properties of ruxolitinib: in a murine model, treatment with ruxolitinib led to improvement in GvHD while maintaining a graft-versus-leukemia effect.[91] This preclinical effect was also observed by Spoerl et al, who could clearly demonstrate the activity of ruxolitinib in the treatment of GvHD and also confirmed that clinically by successfully treating six patients harboring steroid-refractory GvHD with ruxolitinib.[92] This interesting finding was confirmed by observing a complete response rate of 84% in 52 patients with steroid-refractory GvHD in a multicenter setting.[93]

Thus, taken together, there is sufficient preclinical and clinical evidence for an increased risk of infectious complications in treatment with JAK inhibitors, and physicians using these drugs should be alert. Heine et al therefore recently proposed a risk stratification and recommendation in which they propagate an acyclovir and cotrimoxazole prophylaxis as well as a basic screening program prior to beginning ruxolitinib treatment,[94] which from our point of view should be considered, giving the clear evidence mentioned above.

TKIs as Inhibitors of mTOR

The mTOR is a serine/threonine kinase that affects cell growth, proliferation, survival, autophagy, metabolism, and cytoskeletal organization.[95] The mTOR pathway located at a central hub for different signaling cascades plays a pivotal role in the pathogenesis of many malignancies and has thus become a target of interest for therapeutic inhibition. The first drug affecting the mTOR pathway was rapamycin, from which the enzyme draws its name. Rapamycin was originally approved as an immunosuppressant in the United States, yet soon after its approval, its antineoplastic effect was described for a variety of malignancies[96]; however, the clinical benefit of rapamycin has been found to be disappointing, further leading to the development of two drugs targeting mTOR, temsirolimus and everolimus.

Temsirolimus is available in both intravenous and oral formulations and is approved for the treatment of advanced-stage metastatic renal cell carcinoma (RCC) and relapsed or refractory mantle cell lymphoma.[97] Everolimus, which is available as an oral formulation, has been approved by the FDA and the European Medical Agency (EMA) for the treatment of pancreatic neuroendocrine tumors (pNET), advanced RCC, subependymal giant cell astrocytoma associated with tuberous sclerosis, and, in combination with exemestane, for advanced hormone-receptor-positive, HER2-negative breast cancer. In addition, everolimus has also received approval as an immunosuppressant for liver and kidney organ transplantation,[98] and has shown efficacy in treating refractory GvHD.[99]

It is prudent to assume that drugs that are preventing organ rejection predispose to induce infectious adverse effects,

and physicians should be aware of this risk while treating patients with mTOR inhibitors. From a transplant physician's perspective, mTOR inhibitors might be promising. Considering the different options for immunosuppression for solid organ rejection, there is evidence that infectious complications for mTOR inhibitors are less compared to those for classic calcineurin inhibitors such as cyclosporine or mycophenolate mofetil, at least for specific infections such as CMV.[100,101]

The immunosuppressive effects and the risk of opportunistic infections are thus well recognized in solid organ transplantation recipients, but potentially less in patients suffering from solid tumors. As the exposure of patients to these drugs is continuously increasing, more patients are at risk for infectious complications. For temsirolimus, data from the randomized controlled trials clearly suggest a risk of infections for mantle cell lymphoma, where all-grade infections were present in 25% of patients compared to only 9% of patients in the control arm; also the severity of infections was higher.[102] In the pivotal clinical trial, which established temsirolimus as the standard of care for advanced renal cell cancer, the risk of infection for temsirolimus was nearly doubled compared to interferon and the addition of temsirolimus to interferon further significantly increased the infection rate.[103] Combination of temsirolimus and conventional chemotherapy such as temozolomide was also associated with further increased infectious potential.[104]

In the Renal Cell cancer treatment with Oral RAD001 given Daily (RECORD-1) trial, which established everolimus as the drug of choice for patients progressing under anti-VEGF therapy, the number of adverse events as well as infections was significantly higher compared to placebo (37% vs. 18%) with 13% severe infections and several infection-related deaths due to opportunistic infections such as invasive aspergillosis.[105] Indeed, an expert panel recommended to be cautious and aware of infectious complications in patients treated with everolimus, especially if the CD4 cell count is $<200/\mu L$ and recommended a basal screening program to evaluate the antibody immune status of the patient prior to treatment with everolimus.[106] Infectious complications were also observed for pediatric and adolescent patients with tuberous sclerosis treated with everolimus with even fatal course.[107] For patients with hormone-sensitive, advanced breast cancer, two clinical trials analyzed the combination of everolimus with exemestan (Breast Cancer Trials of Oral Everolimus-2 [BOLERO-2] trial)[108] or temsirolimus with letrozole (Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer2 [HORIZON] trial).[109] The addition of the mTOR inhibitor lead to increased infectious adverse events[110] compared to the arm with placebo and aromatase inhibitor. In a large meta-analysis on infectious episodes from 1924 renal cell cancer patients treated with temsirolimus and everolimus in clinical trials, it was shown that infections are twice as frequent and even 2.6 times more frequent for grade 3/4 infections.[111] However, there was no significant difference between temsirolimus and everolimus, suggesting that the observed immunosuppression is class specific and not dependent on the type of mTOR inhibitor. Another recent interesting publication evaluating the occurrence and the grading of infections in patients treated with mTOR inhibitors in clinical trials and comparing these with control patients not receiving mTOR inhibition showed unequivocally that incidence of grade 1–5 infections was significantly higher with single-agent mTOR inhibitors compared with the controls (27% vs. 8%; odds ratio, 4.26; $P < 0.0001$] and also that the clinically relevant grade 3/4 infections were much more frequent. Also, the combination of mTOR inhibitors and chemotherapy further aggravated the incidence and severity of infections compared to single-agent mTOR inhibition.[112]

Indeed, classic opportunistic infections such as *P. jirovecii* pneumonia, which represent a rarity in patients with solid tumors, have been reported in oncologic patients exposed to mTOR inhibitors, underlining the immunosuppressive potential[113,114] of these class inhibitors.

An aggressive diagnostic approach, such as bronchoalveolar lavage for patients with mTOR treatment and pulmonary infiltrates, is recommended as the main differential diagnosis is the frequent noninfectious pneumonitis[115] and the potential microorganisms causing opportunistic infections, such as fungi or *Pneumocystis*, can thus be much more easily diagnosed.

In conclusion, treatment with mTOR inhibitors everolimus and temsirolimus is clearly associated with an increased risk of all-grade and high-grade infections. Indeed, based on the frequency, type, and severity of infections encountered, an antiviral (eg, aciclovir) and even a *P. jirovecii* prophylaxis may be instituted, based on the individual patients' immune status. Although these agents have influenced the therapeutic landscape and armamentarium in various malignancies and thus patients' survival, a heightened awareness even for atypical infections and a stringent diagnostic approach concerning infectious complications is warranted.

Multikinase Inhibitors

In this paragraph, we summarize the potential immunosuppressive properties of multikinase inhibitors, such as sorafenib, sunitinib, regorafenib, axitinib, and pazopanib, as these KIs mediate their effect by targeting several kinases such as vascular endothelial growth factor receptor (VEGFR), PDGFR, FLT-3, c-Kit, and RET. Most studies suggest that the antiangiogenic properties of these multikinase inhibitors are the major contributor to their clinical efficacy, at least in solid tumors. Treatment with sunitinib and sorafenib is associated with a significant increase in neutropenia,[116] and if these cytopenias have an impact on the incidence of infectious complications is not yet clear.

Sunitinib is approved for the treatment of renal cell cancer, GIST, and pNET based on several trials demonstrating its clinical efficacy. Sunitinib's mode of action is believed to be

primarily mediated by antiangiogenic effects.[117] Although it has been recognized that sunitinib induces leukopenia and a potent lymphopenia,[118] the placebo-controlled trials for several malignancies suggest that this finding does not translate into an increase in opportunistic infections[119–122] as infections are rarely reported in the safety data. Sunitinib has been approved since 2006, and thus, a great number of patients have been exposed to this drug until now; reports on infections because of sunitinib treatment are sporadic, suggesting a presumably negligible immunosuppressive potential.

Sorafenib was introduced into the clinical setting in 2005 and is currently approved for palliative treatment of hepatocellular carcinoma (HCC), renal cell cancer, and metastatic thyroid carcinoma[123]; in addition, it has activity in FLT3-mutated leukemias.[124] Compared to sunitinib, myelosuppression and therefore a possible neutropenia is less frequent. Sorafenib treatment affects signal transduction pathways during T-cell activation and even impairs production of interferon gamma independent of the MAPK pathway.[125] It also inhibits the activation and induces apoptosis of peripheral T-cells.[126]

Apparently, this preclinical effect does not seem to translate into a higher rate of infections in solid tumor patients treated with sorafenib. In a recent meta-analysis evaluating postapproval safety data of more than 2000 patients, infections are not reported as significant AEs.[127] Safety data from the large placebo-controlled phase 3 trials suggest a higher noninfection-related AE rate for sorafenib for renal cell cancer[128] in general, but infectious complications were not among them. For HCC, this is equally true, and there are even data that sorafenib has some activity in inhibiting hepatitis C virus, one major and frequent driver in oncogenic transformation to HCC.[129]

On the other hand, a recent multicenter placebo-controlled trial evaluating the effect of adding sorafenib to conventional chemotherapy in patients with de novo AML older than 60 years found a significant increase in infections and infection-related mortality within 60 days after the start of therapy with 15 infection-related deaths in the sorafenib arm versus only 4 in the placebo arm ($P < 0.015$).[130]

These rather conflicting results in myeloid malignancies compared to the data on sorafenib in solid tumor treatment might, in theory, reflect that the (supposedly lymphocyte based) immunosuppressive effect of sorafenib itself is negligible in oncologic patients without prevalent granulocytopenia. In AML patients with long-lasting and profound myelosuppression, the immunosuppression induced by sorafenib affecting the lymphocyte compartment might become more apparent and cause these observed complications.

Regorafenib is a multikinase inhibitor with a very broad spectrum that blocks the activity of several protein kinases, such as VEGFR1, VEGFR2, VEGFR3, TIE2, KIT, RET, RAF1, BRAF, PDGFR, and FGFR.[131] It has been approved for the treatment of advanced colorectal cancer and refractory GIST in 2013 as it has displayed an improvement of survival in these patients in several trials.[132,133] Typical adverse events consist of hand-foot reactions, stomatitis, (noninfectious) diarrhea, and hypertension, but infections are rarely reported.

Although regorafenib targets a myriad of kinases, the literature does not report about an increase in infections, and the number of patients exposed to regorafenib is much less compared to those exposed to sorafenib or sunitinib. The safety data from the placebo-controlled clinical trials do not indicate a heightened prevalence of infection in the study arms with regorafenib, which presumably indicates a marginal effect on the occurrence of infectious side effects.

Pazopanib is a second-generation small-molecule TKI especially targeting VEGFR-1/2/3 while showing a lower affinity against Platelet-derived Growth-Factor receptor (PDGFR)-, FGFR-1/2, and c-KitR. It has shown excellent activity in a variety of malignant diseases such as renal cell cancer[134] and soft-tissue sarcoma,[135] both for which it has been approved, but also in other malignant diseases such as ovarian carcinoma[136] or NSCLC.[137] Similar to regorafenib, data in the literature on potential immunosuppressive side effects leading to infections are almost nonexistent, and the final phase 3 safety data do not imply infectious complications as frequent adverse events.[138]

Lastly, axitinib is a TKI of VEGF, PDGFR-α, and c-Kit and has recently been approved for patients with renal cell cancer refractory to sunitinib or cytokine treatment based on the AXIS trial, which demonstrated an increase in progression-free survival compared to sorafenib[139]; *in vitro* data suggest that axitinib is 40–50 times more potent in inhibiting VEGF, its major target, compared to first-generation multikinase inhibitors.[140] Preclinical data suggest that axitinib has a much less suppressive effect on lymphocytes compared to sunitinib or sorafenib[141]; the (scarce) clinical data on potential infectious complications suggest that this drug seems safe in terms of immunosuppression.

Taken together, the multikinase inhibitors mentioned above, whose main target is the VEGF pathway, are not associated with infectious complications; a finding that can also be observed for bevacizumab, an established antibody targeting VEGF, for whom a potential immunosuppressive effect leading to infectious complications has not yet been observed and for whom a large amount of clinical data is available due to its broad indication and long time past approval.

Inhibitors of the BCR Signaling Pathway

B cells are an essential component of the immune defense because they present antigens, produce neutralizing antibodies, and maintain the lymphoid architecture. For the treatment of B-cell malignancies such as non-Hodgkin's lymphoma (NHL) or even autoimmune diseases such as RA, using pharmacologic agents to target the B cells has shown promising results leading to approval of rituximab, a chimeric anti-CD20 antibody. It has been recognized that infectious complications could be a side effect of prolonged B-cell-depleting treatment,

eg, with rituximab, especially under maintenance therapy,[142] although the exact influence of rituximab on infectious complications is still controversially discussed.[143]

Quite recently, two drugs inhibiting the Bruton's tyrosine kinase (BTK) or the phosphatidylinositol 3-kinase delta (PIK3delta) and thus inhibiting the critical components of the activation of the BCR pathway have emerged and have made a profound impact on the therapeutic landscape of indolent NHL and chronic lymphatic leukemia (CLL).

Ibrutinib, an irreversible inhibitor of the BTK, has shown excellent activity even in high-risk relapsed CLL[144] and mantle cell lymphoma[145] leading to a rapid approval. The second TKI, idelalisib, is targeting another component of the BCR signaling pathway, the PIK3delta; it has also demonstrated significant clinical activity as a single agent in follicular lymphoma[146] and for relapsed CLL in combination with rituximab.[147]

Interestingly, for both of these enzymes, it has been shown that hereditary mutations are associated with an increase in infections. Inactivating mutations of the BTK are the cause of X-linked agammaglobulinemia and lead to deficient development of B lymphocytes, thus causing hypogammaglobulinemia, profoundly reduced levels of serum antibodies, and reduced levels of circulating B cells.[148] BTK deficiency impairs B-cell and also monocytic and dendritic cell functions.[149,150] This leads to a markedly increased incidence and severity of infections often causing even lethal complications.[148] The importance of BTK in the defense against a variety of organisms such as bacteria, virus, and even fungi has been demonstrated preclinically.[151–153] Recently, the so-called activated PI3K-δ syndrome (APDS) was described, which although leading to a gain-of-function mutation of that enzyme; patient-derived lymphocytes had increased levels of phosphatidylinositol 3,4,5-trisphosphate; and phosphorylated AKT protein was prone to activation-induced cell death, thus leading, in fact, to immunosuppression and an increase in, especially, upper airway infections.[154] In addition, patients with this hereditary mutation had a substantial deficiency in naive T cells but an overrepresentation of senescent effector T cells, leading to sinupulmonary infections and viremia due to CMV and/or Epstein–Barr virus.[155] Inhibition of this pathway, however, has also detrimental effects on the immune system, suggesting that there is a strict balance that has to be kept to avoid infections and ensure immune system function.[156]

Based on these preclinical data, it is prudent to assume that there is a substantial potential for infectious complications when affecting these two critical enzymes, and albeit limited, the clinical data support these observations. In the initial phase, 1/2 trial for treatment of lapsed CLL with ibrutinib pneumonia grade 3/4 was observed in 12% of patients and 33% of all adverse events were upper respiratory infections[157]; these occurred typically in the beginning of the treatment, and with continuous neutrophil recovery, the incidence of these events subsided. For patients with high-risk CLL, ibrutinib in combination with rituximab showed grade 3 infections in 13% of patients, with pneumonia the most typical infectious complication.[158] Interestingly, in that study, the investigators observed a trend toward decrease in serum IgM levels and a continuous decrease in CD4+ lymphocytes, which were more than halved after 12 months of treatment, which the authors interpreted as treatment response, as the coevolution and interdependence between T cells and leukemia cells was reduced. In the randomized comparison of ibrutinib versus ofatumumab (the Ibrutinib versus Ofatumumab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia [RESONATE] trial) for relapsed CLL patients, the incidence of infections of any grade was significantly higher in the ibrutinib arm (70% vs. 54%), whereas all-grade infections were similar.[144] These findings suggest that BTK inhibition might be more immunosuppressive than targeting CD20. Lastly, in the trial that leads to the approval of ibrutinib for mantle cell lymphoma, the incidence of upper respiratory tract infections was 23%; however, these were all graded 1 and 2, which, in contrast to treatment in CLL, might reflect the inherently lesser disease-related immunosuppression of mantle cell lymphoma compared to CLL.[145] In a recent trial for patients with Waldenstrom's macroglobulinemia, the rate of infections was slightly less compared to the previous studies (8%), again indicating that the amount of infectious complications is dependent on the underlying disease and its inherent lesser immune system activity.[159] In a recently published analysis of a three-year follow-up of 132 patients with CLL and SLL (small lymphocytic lymphoma) treated with ibrutinib, the rate of overall Infectious side effects and rate of ≥ grade 3 infections was up to 51% in relapsed/refractory patients; due to occurring VZV reactivation, an antiviral prophylaxis was instituted.[160]

For idelalisib, targeting the PIK3delta pathway, the clinical data also suggest an immunosuppressive potential causing infectious side effects. In the initial phase 1 study for CLL patients, serious adverse events were frequently present with ≥ grade 3 pneumonia occurring in 20% and additionally febrile neutropenia and bacteremia occurring in 5.6% and 9.3% of patients with even fatal clinical course.[161,162] Even more striking, two of the identified organisms were *P. Jirovecii*, and even fungal pneumonia was identified in two further patients suggesting that there is a profound inducible immunosuppression associated with idelalisib treatment. Yet, it has to be kept in mind that patients had received intensive treatment regimens such as purine analogues or alemtuzumab prior to idelalisib and CLL itself carries a high risk of infection.[163] In the first-line trial for combination of idelalisib and rituximab in newly diagnosed CLL patients, adverse events occurred frequently, especially pneumonia in 28% of patients, with 19% classified as serious adverse events and also infection-related fatalities.[164] In the large double-blind phase 3 trial analyzing treatment of idelalisib and rituximab compared to rituximab alone for patients with relapsed CLL, the most frequent serious adverse events in the two groups were pneumonia, pyrexia, and febrile

neutropenia.[147] Idelalisib for the treatment of NHL, which by itself probably carries a lower disease-related immunosuppression, was however also associated with infectious complications, especially pneumonia, occurring in 17% of patients in the phase 1 trial[165] and even three infection-related deaths, a finding that was also confirmed in the large placebo-controlled phase 3 trial for follicular lymphoma[146] and, more recently, the phase 1 trial for mantle cell lymphoma.[162]

The potential immunosuppressive properties of inhibitors of the BCR pathway are probably, similar to JAK inhibitors, hinted at by a recent (preclinical) publication regarding its use in treating GvHD. In a murine model of sclerodermatous chronic GvHD, ibrutinib treatment delayed progression, improved survival, and ameliorated clinical and pathological manifestations of mice with GvHD, and the authors found that animals lacking BTK and IL-2 inducible T cell kinase, which is also inhibited by ibrutinib, did not develop cGvHD, indicating that these molecules are critical for its pathogenesis.[166]

So, in summary, the treatment of inhibitors of the BCR signal cascade ibrutinib and idelalisib is associated with infectious complications, the typical manifestation consisting of respiratory infections such as pneumonia. The incidence and severity of these infections is probably dependent on concomitant disease and other immunosuppressants such as steroid treatment in CLL patients, probably representing the group with the highest risk. Individual prophylaxis regimens, such as PcP prophylaxis with cotrimoxazole or antiviral prophylaxis, should be considered in individual patients based on their immune status.

Summary

Infectious complications are a typical treatment-related complication of modern therapies in hemato-oncological treatment regimens. Although often considered as representing just a *pill treatment*, KIs bear the potential of causing severe and even life-threatening infections depending on the pathway involved and the associated off-target kinase activity.

In case of infectious complications, the preclinical and clinical evidence of KIs targeting the angiogenesis or the EGF pathway suggests that these KIs do not aggravate the incidence or the intensity of infections. However, treatment with KIs interfering with critical immune system components such as MTOR inhibitors, JAK inhibitors, or the new KIs affecting the BCR pathways is associated with an increased occurrence of infections and even with the risk of fatal complications. Based on the frequency, type, and severity of infections in patients treated with these drugs, a prophylaxis approach based on individual patient's immune status, concomitant medication (eg, steroids), and comorbidities should be considered. A heightened awareness and a stringent diagnostic approach should be instituted in these patients as life-threatening infections may occur.

Author Contributions

Conceived and designed the experiments: MR, DB. Analyzed the data: MR, DB, TB. Wrote the first draft of the manuscript: MR. Contributed to the writing of the manuscript: MR, DB, TB, WKH. Agree with manuscript results and conclusions: MR, DB, TB, WKH. Jointly developed the structure and arguments for the paper: MR, DB, WKH. All authors reviewed and approved of the final manuscript.

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