Tyrosine-Kinase Inhibitors

15

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Introduction

Tyrosine kinases are a family of membrane-bound or intracellular molecules that regulate a variety of important cellular functions. They are involved in transferring phosphate groups to tyrosine residues in substrate proteins transducing intracellular signals engaged in many cellular functions, including the modulation of growth factors related to carcinogenesis. Many tyrosine kinase inhibitors (TKIs) play a key role in cell cycle regulation and carry significant potential for oncogenesis if mutated [1]. As such, protein kinases have become one of the most intensively investigated target classes for therapeutic intervention with consensus guidelines for clinicians who care for immune compromised hosts [2]. So far, more than ten classes of small molecular weight protein kinase inhibitors have been approved for cancer treatment, and over 100 kinase inhibitors are currently in clinical development [3].

The first TKI, imatinib, was approved in 2001 as an inhibitor of breakpoint cluster region (BCR)-v-abl Abelson murine leukemia viral oncogene homolog (ABL) tyrosine kinase fusion protein (BCR-ABL). It represents the first-in-class agent targeting this specific mutation and subsequently spawned a new class of targeted therapies [1]. There are now many other approved TKIs for patients with hematologic or other malignancies. In this chapter, we review this family of small molecules with special attention to BCR-ABL TKI inhibitors. We also highlight the unique features of TKIs and focus on their specific indications, the risks of infection and recommendations for prophylaxis.

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The Tyrosine Kinase Inhibitor Family

Tyrosine kinases are involved in intracellular signaling cascades and play a crucial role in initiating or perpetuating a signaling cascade within the cell, leading to cell growth, transformation, activation, or apoptosis. Inhibitors of these enzymes, known as TKIs, are small molecules that have been considered as "targeted therapies" because of their specific mechanisms of action [4] as seen in (Fig. 15.1). The tyrosine kinases are often selectively overexpressed in malignancies due to point mutations or chromosomal rearrangements. Hence, TKIs have mostly been developed for the treatment of malignancies. TKIs have good oral bioavailability and may be prone to cytochrome P450 drug-drug interactions [5, 6]. TKIs, because of their unique mechanism of action, have the potential to increase the risk of several infectious complications, which are detailed in Table 15.1.

BCR-ABL Inhibitors

There are currently five agents in this class—imatinib, dasatinib, nilotinib, bosutinib, and ponatinib—which are all used to treat primary hematologic malignancies that arise as a result of the BCR-ABL gene and fusion protein. BCR-ABL inhibitors also target other receptor tyrosine kinases and a wide range of non-receptor kinases [7]. They all share a common mechanism of binding to the ATP-binding site of the mutant BCR-ABL fusion protein with high affinity.

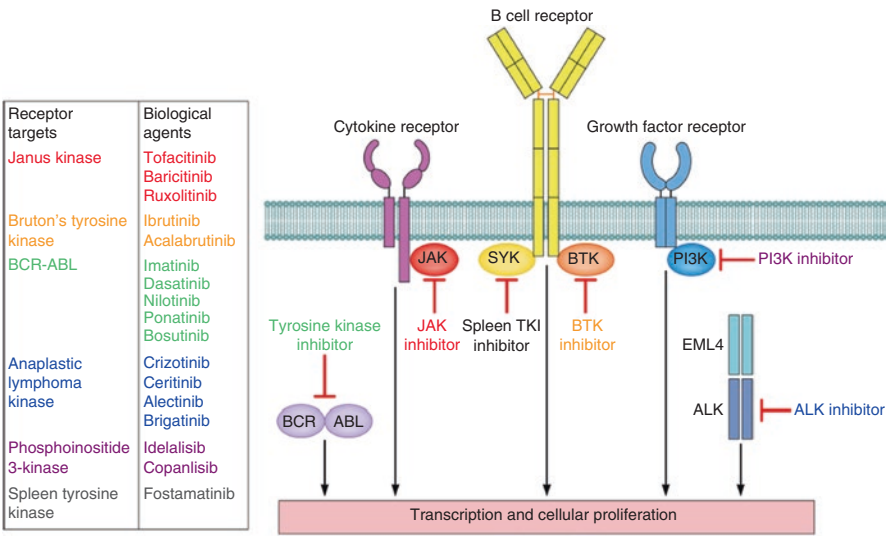

Fig. 15.1 Action points of specific TKI [with permission from Davis et al.]

Mechanism of Action (MOA) and Indications

Imatinib was the first TKI approved for chronic myelogenous leukemia (CML). It competitively inhibits the ATP-binding site of the BCR-ABL tyrosine kinase, inhibiting the phosphorylation of tyrosine proteins involved in BCR-ABL signal transduction. It also specifically acts on the receptor for platelet-derived-growth factor (PDGFR) and c-KIT tyrosine kinases. As a result, it is also clinically useful for certain diseases such as gastrointestinal stromal tumors (GIST) and systemic mastocytosis, as well as diseases such as hypereosinophilic syndromes (HES) and chronic myelomonocytic leukemia (CMML) [1].

Dasatinib is a second-generation inhibitor of BCR-ABL kinases approved for the treatment of Ph + CML or acute lymphocytic leukemia (ALL) [8–10]. It was

Table 15.1 Summary of tyrosine kinase inhibitors

Tyrosine kinase inhibitor	Mechanism of action	Indication	Pathophysiology of infection	Infection risk
BCR-ABL inhibitor				
Imatinib	Competitive inhibitor of Bcr-Abl, PDGFr, c-kit	CML, GIST, MDS, Eos leukemia HES, mastocytosis	Induces neutropenia, Inhibits T-cell proliferation And activation Reduces specific CD8+ responses and cause Dysfunction of dendritic Cells	Higher neutropenia risk Mild upper respiratory infections Usually in first year Increased risk of VZV, HBV Rare cases of fungal and TB infection
Dasatinib	Dual SRC/ ABL inhibitor, TEC family kinases, and BTK	Ph + CML, Ph + CLL		**Higher risk of infection than imatinib** CMV reactivation with HSCT
Nilotinib	Selective, competitive inhibitor of Bcr-Abl **More potent than imatinib**	Ph + CML		Less risk of infection
Bosutinib	Competitive inhibitor of Bcr-Abl	Ph + CML		Higher neutropenia risk **Pleural effusion** Pneumonia
Ponatinib	Competitive inhibitor of Bcr-Abl	Ph + CML or **T315I mutant** CML or ALL		Higher neutropenia risk Limited data

(continued)

Table 15.1 (continued)

Tyrosine kinase inhibitor	Mechanism of action	Indication	Pathophysiology of infection	Infection risk
JAK inhibitor				
Tofacitinib	Competitive inhibitor of JAK1, 2,3	RA, PsA, UC	Reduce T-cell number and function, inhibit T-cell proliferation, and impair NK cell maturation	Increased risk of mild infection, usually pneumonia, SSTI, HZ Serious infection was 3.1 events/100 patient-years
Baricitinib	Selective and reversible JAK1 and 2 inhibitor	RA		**Highest risk for HZ**
Ruxolitinib	Inhibitor of JAK1 and 2	MF, PCV		HZ, tuberculosis
Upadacitinib	Selective JAK1 inhibitor	Moderate to severe RA refractory to MTX		Limited data
BTK inhibitor				
Ibrutinib	Selective, reversible inhibitor of BTK protein	CLL, SLL, MCL, WM, MZL, cGVHD	Primary B cell dysfunction	Neutropenia **Pneumonia**, **URTI**, SSTI IFI
Acalabrutinib	Irreversible BTK inhibitor	MCL		Grade 3 or 4 infections
PI3K inhibitor				
Idelalisib	Reversible inhibitor of PI3K-δ	CLL, SLL, FL	B- and T-cell dysfunction	**Fatal pneumonia or sepsis** PJP, IFI
Copanlisib	Second generation, PI3K-α and δ isoforms	FL		Pneumonia PJP IFI

Table 15.1 (continued)

Tyrosine kinase inhibitor	Mechanism of action	Indication	Pathophysiology of infection	Infection risk
ALK inhibitor				
Crizotinib	ALK or ROS1	NSCLC	Not specified	No significant increase in risk of infection **Interstitial pneumonitis** **Increased risk for infected complex renal cysts**
Ceritinib	ALK	Locally advanced or metastatic NSCLC		None reported
Alectinib	ALK	Advanced or previously treated NSCLC		**Nasopharyngitis**
Brigatinib	ALK	Advanced NSCLC		None reported
SyK inhibitor				
Fostamatinib	Intracellular SyK inhibitor	ITP, RA	Regulates both T-cell and B-cell expansion and proliferation; diminished proliferation of antigen-specific CD4+ T cells and reduced production of inflammatory cytokines such as IFN λ and IL-17	Neutropenia. No significant increase in infection risk

ALK anaplastic lymphoma kinase, *BCR-ABL* breakpoint cluster region (BCR)-v-abl Abelson murine leukemia, *BTK* Bruton tyrosine kinases, *JAK* Janus-associated kinase, *PI3K* phosphatidylinositol 3-kinase inhibitors, *SYK* spleen tyrosine kinase
In bold—unique features of the drug/class

developed as a dual SRC/ABL inhibitor, but it also affects a wider array of kinases, including TEC family kinases and Bruton tyrosine kinase (BTK) [11]. This increase in off-target activity may be responsible for in vitro data that hint at a strongest immunosuppressive effect for this TKI [12].

Nilotinib is a second-generation BCR-ABL inhibitor that is also approved for use in the treatment of Ph + CML [13, 14]. It is an analogue of imatinib with more potent BCR-ABL kinase inhibition.

Bosutinib is a small, orally bioavailable molecule, inhibiting both SRC and BCR-ABL with activity against imatinib-resistant CML cell lines [15]. It is approved for use in various phases of CML [16, 17]. Bosutinib has demonstrated activity and manageable tolerability in a phase I/II study of patients with chronic phase CML following resistance/intolerance to imatinib only, or imatinib plus dasatinib and/or nilotinib [15, 18–20].

Ponatinib is a TKI active against disease resistant to other BCR-ABL TKIs [21]. It is approved for use in patients with CML or PH+ ALL resistant to other therapies, or with the T315I mutation.

Risk of Infection

Imatinib is known to induce neutropenia, inhibit T-cell proliferation and activation, reduce specific CD8+ responses to CMV and EBV, and cause dysfunction of dendritic cells [22–24]. The phase 3 IRIS study in 2003 [25] using imatinib as initial treatment of newly diagnosed chronic phase CML among 553 patients showed 60.8% all-grade neutropenia with imatinib, of which only 14.3% were grades 3 (i.e., neutrophil count between 500–1000/mm^3 and 4 (neutrophil count <500/mm^3), based on the Common Toxicity Criteria of the National Cancer Institute. Mild respiratory infections were commonly low grade and viral in origin. Long-term data showed that nearly all infection complications occurred within the first year. Only 1 patient each was reported as having treatment-related neutropenia, febrile neutropenia, and an anorectal infection in the first year of treatment, whereas only 1 patient each developed appendicitis and cellulitis in years 6 and 11, respectively [26].

Patients receiving imatinib for GIST did not have significant infection risk, although grade 3 or higher neutropenia occurred in 7% [27, 28]. There were also no significant infectious complications in a phase II study investigating its use in other malignancies [29].

However, long-term experience with imatinib has demonstrated increased risk of HBV or VZV reactivation, occurring in 2% of patients in a single retrospective study [30]. In another, 13–16% of patients developed a variety of infections, most commonly VZV and pneumonia [31]. Sporadic cases of tuberculosis [9, 32, 33], leishmaniasis [34], *cryptococcosis*, and other fungal infections have also been reported [35, 36].

Dasatinib appears to be associated with a greater risk of infection compared to other BCR-ABL inhibitors. In a clinical trial [37], infections of any grade occurred in 27 (11%) of dasatinib-treated patients compared to 18 (7%) imatinib-treated patients. Five patients versus 1 patient died due to infection, in the dasatinib and imatinib arm, respectively; however, the investigators deemed these infections unrelated to the drug. Interestingly, the majority of infections did not occur during the period of neutropenia.

In a safety analysis of two major clinical trials [38] inclusive of 1150 patients, serious infections were rare and only one grade 3–4 opportunistic infection was observed for dasatinib. However, a comparative analysis of dasatinib with nilotinib demonstrated that there was a higher proportion of infection-related healthcare resource utilization costs among those receiving dasatinib than in those receiving nilotinib, largely attributable to a larger proportion of infection-related inpatient-days [39].

The risk of CMV reactivation appears to be increased following hematopoietic stem cell transplantation (HSCT); in one study of 109 patients, dasatinib was associated with an increased incidence of CMV reactivation in the first year after transplantation (adjusted hazard ratio = 7.65, 95% CI, 1.84–31.7) [40].

Nilotinib was not associated with a greater risk of infection and caused less neutropenia compared to imatinib among patients with newly diagnosed CML. This was corroborated by subsequent cohorts [41–43]. Phase II studies examining its use in treated patients with chronic phase CML also failed to demonstrate evidence of significant infections, although neutropenia more commonly occurred [44, 45].

In a review of 169 patients with CML receiving first-line nilotinib therapy or therapy after imatinib failure, 9 (10%) patients among the frontline therapy group developed any infection, whereas 29 of 79 (37%) patients treated with nilotinib after imatinib failure developed any infection [46].

Phase I/II studies of *bosutinib* monotherapy in patients with imatinib-resistant chronic phase CML found no evidence of infectious complications but reported grade 3 or higher neutropenia in 18% of patients [15]. On long-term follow-up of this cohort [47], serious adverse events (SAEs) occurred in 59% (99/167) of patients with the most frequently occurring individual SAEs (>5% of patients overall) being pneumonia (10%), pyrexia (7%), febrile neutropenia (6%), thrombocytopenia (6%), disease progression (5%), headache (5%), and pleural effusion (5%). The only newly occurring individual SAE reported in more than two patients within year 2, 3, or 4 was pneumonia (three patients with events in year 2).

Ponatinib is relatively new, and post-marketing surveillance is limited. However, in phase II studies investigating its use in previously treated patients with CML or ALL did not demonstrate increased risk for infectious complications, although grade 3 or 4 neutropenia occurred in 12–26% [48], or in 14% of patients, respectively [49].

Prevention of Infection

Given the potentially increased risk of HBV reactivation infection among patients treated with TKIs, all patients should be screened for HBV prior to starting treatment [7] (Table 15.2). Those with evidence of HBV infection should initiate antiviral therapy or prophylaxis with entecavir or tenofovir, which should continue up to 6–12 months after cessation of immune suppressive therapy [50]. Susceptible patients should be vaccinated according to society guidelines [51], although the response may be impaired because of the underlying condition or because of the TKI.

Janus-Associated Kinases (JAK) Inhibitors

JAKs are a family of four non-receptor protein tyrosine kinases—JAK1, JAK2, JAK3, and tyrosine-kinase 2—which mediate signaling of cytokine receptors [52]. The pathways are involved in the growth, development, and differentiation of various cells but are crucial to the function of immune and hematopoietic cells [53]. There are three currently available JAK inhibitors—tofacitinib, baricitinib, and ruxolitinib. Their mechanisms of action, indications, and infection risk are summarized in Table 15.1.

Table 15.2 Recommendations for screening and prophylaxis

TKI class	Screening/monitoring	Prophylaxis	Vaccination
TKI	Hepatitis B	Consider treatment of chronic hepatitis B (HbsAg+) up to 6–12 months after cessation of therapy	Routine, age-appropriate vaccination
JAK	LTBI Hepatitis B	No specific recommendations	VZV vaccine
BTK	Hepatitis B	Consider PCP or other fungal prophylaxis if heavily treated or with prior exposure Chronic hep B (HbsAg+)	Influenza, pneumococcal vaccines
PI3K	Hepatitis B LTBI *Monitoring* CMV (monthly) ANC (q2 weeks)	Universal prophylaxis for PJP During treatment and for 2–6 months after cessation of therapy	Influenza, pneumococcal vaccines
ALK	No specific recommendations		
SyK	No specific screening recommendations Monitor ANC monthly	No specific recommendations	

ALK anaplastic lymphoma kinase, *BCR-ABL* breakpoint cluster region (BCR)-v-abl Abelson murine leukemia, *BTK* Bruton tyrosine kinases, *JAK* Janus-associated kinase, *PI3K* phosphatidylinositol 3-kinase inhibitors; SyK, spleen tyrosine kinase [10, 11]

MOA and Indication

Tofacitinib is a reversible competitive inhibitor of JAK1, JAK2, and JAK3 that inhibits lymphocyte proliferation and cytokine production, affecting the maturation of monocyte-derived dendritic cells and capacity to stimulate T cells [54, 55]. It was approved by the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) [56, 57].

Baricitinib, the second JAK inhibitor approved by the FDA for use in the treatment of RA [58, 59], is a selective and reversible JAK1 and 2 inhibitor. It suppresses the differentiation of plasmablasts, Th1, and Th17 cells [60]. *Ruxolitinib* is an inhibitor of JAK 1 and 2, approved for treatment of myelofibrosis and polycythemia vera (PCV) [61, 62]. *Upadacitinib*, a selective JAK-1 inhibitor, was recently approved in 2019 for the treatment of moderate to severe RA nonresponsive to methotrexate.

Risk of Infection

All JAK inhibitors may reduce T-cell number and function, inhibit T-cell proliferation, and impair NK cell maturation, which may be responsible for the increased risk of infectious complications [63]. In general, JAK inhibitors are associated with an increased risk of mild infections, such as respiratory tract infections, a small but increased risk of serious infections (3 per 100 patient years), and a consistent signal for a heightened risk for herpes zoster and tuberculosis [64].

In a review of pooled data from phase 2, phase 3 (P2P3), and long-term extension (LTE) studies of tofacitinib, among 4789 patients with RA, the overall rate of

serious infection was 3.1 events/100 patient-years [65]. Age, corticosteroid dose, diabetes, and tofacitinib dose were independently linked to the risk of serious infection. Lymphocyte counts of $<0.5 \times 10^3/mm^3$ were rare but were associated with an increased risk of treated and/or serious infection. The most frequent infection was pneumonia, but skin and soft tissue infections were also commonly reported. Nonserious or serious herpes zoster virus infections were reported in 346 patients in the P2P3LTE population (incidence rate 4.27 events per 100 patient-years [95% CI 3.85–4.75]), while only 25 patients experienced an opportunistic infection (0.30 events per 100 patient-years [95% CI 0.20–0.44]). TB was reported in 16 patients (6 cases in the pooled P3 population [all receiving higher-dose tofacitinib at 10 mg twice daily], and 10 in the LTE group [5 receiving tofacitinib at a dosage of 5 mg twice daily and 5 receiving tofacitinib at a dosage of 10 mg twice daily]). The risk of serious infection did not increase over time with an incidence rate of 3.09 events/100 patient-years at 8.5 years follow-up.

Twenty-one studies were included in a recent meta-analysis [66] specifically evaluating the risk of serious infection and herpes zoster among RA patients receiving JAK inhibitors—11 tofacitinib (5888 patients), 6 baricitinib (3520 patients), and 4 upadacitinib studies (1736 patients). For serious infections, the incidence rates were relatively low at 1.97 (95% CI: 1.41, 2.68), 3.16 (95% CI: 2.07, 4.63), and 3.02 (95% CI: 0.98, 7.04), respectively. For herpes zoster, the incidence rates were 2.51 (95% CI: 1.87, 3.30), 3.16 (95% CI: 2.07, 4.63), and 2.41 (95% CI: 0.66, 6.18), respectively. The risk of herpes zoster appears to be higher overall than the general population, and it was numerically greatest with baricitinib.

Prevention of Infection

Screening for and treatment of latent tuberculosis infection and hepatitis B infection are advised in all patients before commencing treatment (Table 15.2). Given the higher risk of varicella zoster virus (VZV), vaccination against VZV with recombinant vaccine should also be considered for patients with positive serology or prior history of illness 2–3 weeks prior to starting therapy [67] (Table 15.2).

Bruton's Tyrosine Kinase (BTK) Inhibitors

BTK is a non-receptor protein kinase expressed in B cells, myeloid cells, mast cells, and platelets. B-cell receptor (BCR) signaling via BTK is imperative for B-cell activation, proliferation, and survival (945). There are two currently approved agents in this class – ibrutinib and acalabrutinib (Table 15.1).

MOA and Indication

Ibrutinib is a selective and reversible inhibitor of the BTK protein, approved for the treatment of CLL, small lymphocytic lymphoma (SLL), and mantle cell lymphoma (MCL), Waldenstrom's macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic graft versus host disease (cGVHD) [68, 69].

Acalabrutinib is an irreversible BTK inhibitor for the treatment of MCL. The highly selective and potent BTK inhibition provided by acalabrutinib is thought to translate into an improved safety profile compared with other targeted therapies [70, 71].

Risk of Infection

Infections in patients treated with ibrutinib relate primarily to B-cell dysfunction [72]. However, invasive fungal infection has also frequently been reported in association with BTK inhibitors, possibly as a result of its off-target effect on other kinases [72, 73].

In one study [74], 70% of 195 patients with relapsed or refractory CLL/SLL treated with ibrutinib developed an infection. Neutropenia occurred in 42 patients (22%), and pneumonia and urinary tract infections occurred in 14–17%.

The use of ibrutinib as first-line therapy for CLL/SLL was not clearly associated with an increased risk of infection in clinical trials, although severe pneumonia did occur [75]. In another study of 64 patients given ibrutinib for relapse or refractory MZL, 19% of patients experienced grade 3 or higher infections, most commonly pneumonia (8%) and cellulitis (5%) [76].

In a meta-analysis of prospective studies evaluating the use of ibrutinib among patients with a lymphoid malignancy [77], infectious complications were reported in almost all (44/48, 92%) trials. Infectious adverse events of any grade occurred in 56% of patients (approximately $N = 900$) treated with single-agent ibrutinib and in 52% of patients (approximately $N = 250$) receiving combination therapy. Grade 3–4 infectious adverse events occurred in 26% of patients on a single agent, and 20% of patients receiving combination therapy. The rate of grade 5 infectious adverse events was 2% in both cohorts. Eighteen of 22 single-agent trials and 15 of 28 combination therapy trials noted grade 3–4 pneumonia. The patient-affected rates for grade 3–4 pneumonia were 13% in single-agent studies and 8% in the combination setting. Grade 5 pneumonia occurred in 2% of all patients. These fatal infectious events included opportunistic pathogens such as *Pneumocystis jirovecii*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, *Nocardia* species, and *Aspergillus* species.

In a more recent systematic review of phase III randomized controlled trials only [78], (7 studies, $n = 2167$ patients), ibrutinib was associated with a significantly increased risk of infection (any grade and grade 3–5) in patients with B-cell malignancies [pooled risk ratio (RR) = 1.34, 95% confidence interval [CI], 1.06–1.69, $P = 0.015$; and RR = 1.35, 95% CI, 1.05–1.74, $P = 0.018$, respectively]. In patients with CLL, a significantly increased risk of grade 3–5 infection was noted in the ibrutinib group [pooled RR = 1.24, 95% CI, 1.02–1.50, $P = 0.028$]. Pneumonia and URTI were the two most commonly reported infections in the studies included in this analysis.

A recent study looked at 124 patients treated with acalabrutinib in the phase II ACE-LY-004 trial [70], who were adjusted to match average baseline characteristics of populations from studies using alternative targeted treatment regimens for relapsed/refractory MCL for either monotherapy or combination therapies. The overall safety profile of acalabrutinib was similar to or better than that of the

monotherapies; however, there was an increased risk of grade 3/4 infections versus the combination bendamustine + rituximab, and an increased risk of anemia compared with lenalidomide + rituximab and ibrutinib + rituximab.

Prevention of Infection

Recommendations for antifungal prophylaxis are currently not well defined. Further systemic and large-scale evaluation of the risk for pneumocystis pneumonia and other fungal infections are required before formal guidance can be issued. In general, pneumocystis prophylaxis may be given to those who have received prior chemoimmunotherapy, have refractory disease, or other risk factors such as concomitant high-dose steroid use [79, 80]. All patients should be screened for serological evidence of hepatitis B virus prior to commencement of ibrutinib, with prophylaxis provided to those who are hepatitis B surface antigen positive [81]. Vaccination against influenza and pneumococcus is recommended prior to initiation of therapy, but immune response is typically poor because of the underlying condition [82–84] (Table 15.2).

Phosphatidylinositol 3-Kinase (PI3K) Inhibitors

Phosphatidylinositol 3-kinase (PI3K) is a signaling pathway activated downstream of BCR. Along with protein kinase B (AKT) and mammalian target of rapamycin (mTOR), it is responsible for B-cell proliferation, cell survival, and angiogenesis [85]. There are two currently available agents in this class—idelalisib and copanlisib.

MOA and Indication

*Idelalisib i*s a reversible inhibitor of PI3K-δ and is approved for use in the treatment of CLL, SLL, and follicular lymphoma (FL) [86–88]. Inhibition of PI3K-δ impairs both B- and T-cell-mediated function [81, 89, 90].

Copanlisib is a second-generation, intravenous PI3K inhibitor with predominant activity in PI3K-α and δ isoforms [91] approved for relapsed FL.

Risk of Infection

Pneumonia is one of the most common infectious complications associated with idelalisib use, with an incidence of about 20%; majority are grade 3 or higher [92]. Atypical infections, such as pneumocystis pneumonia, invasive fungal infection, and noninfectious (autoimmune) pneumonitis also occur [93].

In a retrospective analysis among 2198 patients receiving idelalisib [94], the overall incidence of pneumocystis pneumonia infection was 2.5% in patients receiving idelalisib, with or without rituximab, with or without bendamustine, compared to only 0.2% in patients receiving only rituximab with or without bendamustine. In this cohort, pneumocystis pneumonia prophylaxis reduced the incidence from 3.4% to 1.3%.

Fatal and serious infections have been reported in 21–48% of patients receiving idelalisib [86], and a warning was issued related to this risk. The increased risk of

infection related death from either sepsis or pneumonia frequently occurred within the first 180 days of starting treatment [95]. Given this substantial risk, the FDA recommended that it is not indicated for first-line treatment of malignancy or in combination with bendamustine and/or rituximab for patients with FL [86].

Two phase II studies have evaluated the infection profile of copanlisib; in the smaller study [96] (n = 33), neutropenia occurred in 34.5% with grade 3 or higher neutropenia in majority (29.8%); infections were reported in 64.3% of patients, with grade 3 or higher infections including pneumonia in 14.3%, febrile neutropenia in 3.6%, and urinary tract and skin and soft tissue infections in 2.4%. In the larger study (n = 142) [97], pneumonia occurred in 21% of patients overall, and 15% experience grade 3 or higher pneumonia. In both cohorts, infection from unusual organisms such as *P. jirovecii*, *C. neoformans*, and *Aspergillus* species also occurred.

Prevention of Infection

Universal prophylaxis against *P. jirovecii* is recommended for all patients during treatment and for 2–6 months after cessation of idelalisib therapy [81] (Table 15.2). Monthly preemptive monitoring for CMV among those with positive IgG serology is also recommended upon initiation of idelalisib treatment [86–88]. Monitoring of absolute neutrophil count should be monitored at least every 2 weeks for the first 6 months of treatment, and the drug should not be started in patients with an ongoing or active infection [86–88]. Screening for latent TB infection and HBV are also recommended although there is insufficient data regarding the risk of reactivation infection. Both pneumococcal and influenza vaccination are also recommended [98]. Until further data are available, the recommendations for idelalisib should also be applied to copanlisib (Table 15.2).

Anaplastic Lymphoma Kinase (ALK) Inhibitors

The ALK gene codes for the ALK receptor tyrosine kinase whose exact function is unknown but may be related to neuronal cell proliferation [64]. Activation of this gene usually occurs via chromosomal rearrangement, and ALK rearrangements are seen in 3–5% of non-small cell lung cancers (NSCLC), most commonly in adenocarcinomas.

MOA and Indication

Crizotinib was the first ALK inhibitor approved for the treatment of advanced non-small cell lung carcinoma (NSCLC) with an ALK or ROS1 gene rearrangement [99–101]. The other ALK inhibitors currently approved for use are summarized in Table 15.1.

Risk of Infection

Data from two randomized controlled trials [102, 103] did not show evidence of increased risk of infection with crizotinib, although neutropenia occurred in 11–13%

of patients. Upper respiratory tract infections also occurred at a higher rate but were not associated with significant morbidity or mortality [102]. A unique feature of crizotinib is the propensity to develop complex renal cysts, which may be secondarily infected [104]. Interstitial pneumonitis has also been reported with all ALK inhibitors [103, 105–108].

Prevention of Infection

At this time, there are no specific recommendations regarding prevention of infectious complications from the use of ALK inhibitors.

Spleen (Syk) TKI

Spleen tyrosine kinase (Syk) is an intracellular cytoplasmic tyrosine kinase that is widely expressed in hematopoietic stem cells, particularly B cells [109]. It also plays a pivotal role in signaling and activating Fc receptors [110], regulating both T-cell and B-cell expansion and proliferation, and mediating signaling in inflammatory cells [111]. In vitro, Syk inhibition leads to diminished proliferation of antigen-specific CD4+ T cells and reduced production of inflammatory cytokines such as IFN λ and IL-17 [112].

MOA and Indication

Fostamatinib is the only currently approved agent in this class for use in patients with chronic immune thrombocytopenia (ITP) [113]; it is used off label for RA [111]. Its active metabolite, R406, inhibits signal transduction by Fcγ receptors involved in the antibody-mediated destruction of platelets by immune cells in chronic ITP [110], which results in increased platelet counts in this population.

Risk of Infection

Given the role of Syk in the immune response, one would expect its inhibition to have the potential to make the patient critically ill, but this has not been the case thus far [64]. Early phase II studies in patients receiving fostamatinib reported dose-related neutropenia in 6 [109] to 15% [114] of patients, higher than those receiving placebo.

In a small phase II study of 16 patients with chronic, refractory ITP [115], the use of various doses of fostamatinib led to a small but statistically significant decrease in total WBC, without increasing the infection risk. Two paired phase III studies compared fostamatinib with placebo using different doses [116], and rates of moderate to severe infections were similar compared to placebo at 8% vs. 6%. The risk of mild respiratory infections was slightly higher for patients on fostamatinib at 11% compared to 6% of those on placebo.

Prevention of Infection

There are currently no specific recommendations about preventive measures for patients taking fostamatinib. However, monthly monitoring of the absolute

neutrophil count is recommended, with dose reduction or temporary cessation of the drug if it falls to $<1 \times 10^9$/liter [113].

Conclusion

Several TKI are now available for use as primary therapy for hematologic malignancies and autoimmune diseases and has made the treatment of these diseases easier and more successful. However despite this targeted approach, the risk of infection remains, and is higher for those with refractory disease and those with history of prior immune suppression. The types of infection differ depending on the TKI class, although infection risk with TKIs appears to be related to the degree of neutropenia, and include viral or fungal pneumonia and other respiratory tract infections. Reactivation infections, such as tuberculosis and hepatitis B, can also occur, and a thorough evaluation and screening of these patients prior to initiation therapy must be performed.

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