Kinase Inhibitors in Large Cell Lymphoma

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15.1 Introduction

Regulation of a broad array of cellular functions in both normal cells and cancer is controlled through the phosphorylation of unique proteins within multistep signaling pathways. Phosphorylation is directed through hundreds of specific kinases which can be activated through a variety of mechanisms. Not surprisingly, these tightly regulated networks are critical to nearly all cellular functions and can be abnormally activated or suppressed in cancer through both genetic and epigenetic mechanisms [1]. Often, these alterations in kinase activity result in tumorigenic changes leading to increased survival and resistance, as well as tumor growth and spread (Fig. 15.1). It has also become evident that aberrant kinase activity plays a central role in a tumor's ability to evade immune surveillance. As a result, kinase inhibition has emerged as a field of intense study across multiple cancer subtypes, and currently over 25 oncology drugs that target kinases are approved in the United States [1].

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Recently, insights into important kinase-controlled pathways in aggressive B-cell malignancies have led to the development of several inhibitors with potential in lymphoma. Unfortunately, due to the overlapping and redundant nature of most signaling cascades, single agent activity has been low, resistance is common, and most patients still relapse following initial response. Toxicity has also been difficult to predict, likely due to the ubiquitous nature of several targets and their multifunction role across cell types. Despite these setbacks, promising kinase-based combinations are emerging, and research on predictive biomarkers is underway.

This chapter will review some of the current classes of tyrosine kinase inhibitors being studied in aggressive B-cell lymphomas, along with recent clinical outcomes seen with the leading novel agents in each class.

15.2 The B-Cell Receptor Pathway

The B-cell receptor (BCR) pathway is essential for the development of both normal B cells and their malignant brethren. The B-cell receptor consists of a highly variable extracellular antigen-binding domain and an intracellular cytoplasmic tail consisting of immunoreceptor tyrosine-based activation motifs (ITAMs) which further generate intracellular signals [2]. The initiation/activation and maintenance of BCR signaling appear to

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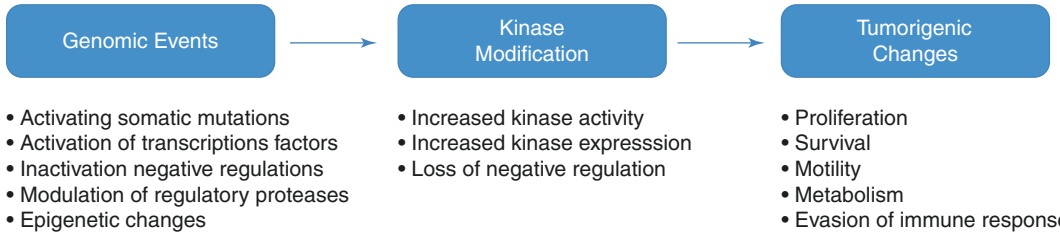

Fig. 15.1 Kinase alterations in aggressive lymphoma

differ in subtypes of aggressive B-cell malignancies, and interruption of this pathway through inhibition of critical kinases represents a viable strategy for targeting aggressive B-cell lymphomas [3]. Although the exact mechanisms of pathway activation are still being elucidated, activated B-cell (ABC) DLBCL likely depends on "chronic active" BCR signaling mediated through receptor clustering, while germinal center B-cell (GCB) DLBCLs may be stimulated in an antigen-independent manner through receptor cross-linking leading or "tonic" signaling [4, 5]. Furthermore, gain-of-function mutations in the BCR subunit CD79 occur more frequently in ABC subtype compared to GCB.

15.2.1 BTK Inhibitors

Bruton's tyrosine kinase (BTK), a member of the TEC family kinases, lies proximal in the BCR and is required for pathway signaling. BTK is activated by Src family kinases Blk and Lyn and phosphorylates phospholipase Cy (PLC gamma). Signaling through BTK eventually leads to downstream activation of both NF-kB and MAP kinase pathways [6]. Inhibition of BTK as a therapeutic strategy has been extremely successful in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma and has modest but consistent activity in aggressive large cell lymphomas.

15.2.1.1 Ibrutinib

Ibrutinib is an oral, covalent irreversible inhibitor of BTK. Initial phase I studies of ibrutinib reported responses in two of seven DLBCL patients [7]. A subsequent phase I/II study by Wilson and colleagues enrolled patients with both relapsed ABC and GCB diffuse large B-cell lymphoma. The study enrolled 80 patients, including 54% of patients who were refractory to prior therapy and 23% who had failed a prior stem cell transplant. All patients received standard dosing with 560 mg once daily. The overall response rate across subtypes of DLBCL was 22% including 9% of patients who achieved a complete remission. Progression-free survival was 5 months. As part of the initial study design, all patients underwent analysis of their primary tumor by gene expression profiling to determine the cell of origin. Interestingly, although patient characteristics were common between groups, inhibition of BTK was dramatically different between subtypes of DLBCL. Patients with ABC DLBCL achieved an overall response rate of 37%, including 16% who achieved complete remission. The response rate in GCB DLBCL was only 5%. Furthermore, ABC lymphomas with mutations in the BCR were especially sensitive to ibrutinib therapy with an overall response rate of 56%. Common toxicities associated with ibrutinib include fatigue, atrial fibrillation, bruising, and hypertension [8]. A subsequent phase Ib study combined ibrutinib with R-CHOP in patients with untreated DLBCL. Younes and colleagues reported a 94% overall response rate with the combination without an evident increase in toxicity [9]. Phase III studies of R-CHOP with or without ibrutinib in DLBCL are underway.

15.2.1.2 Tirabrutinib

Tirabrutinib (ONO-4059) is a selective and reversible inhibitor of BTK with a 50% inhibitory concentration (IC50) of 2 nmol/L and an

IC50 of greater than 300-fold selectivity for other kinases. Of the 35 patients with DLBCL recruited in the phase I trial, 31 were classified as ABC DLBCL using the Hans immunohistochemical algorithm. Median number of prior treatments was three (range two to ten), and 30/35 patients were refractory to their last line of chemotherapy. 11/31 (35%) of ABC subtype responded with two confirmed complete responses and one CRu. Median time on treatment was 12 weeks. Tirabrutinib was generally very well tolerated. The most common (75%) were grade 1 or 2 in severity. Grade 3 or 4 toxicities were mainly hematological, occurred early during therapy, and recovered spontaneously. There were no grade 3 or 4 episodes of hemorrhage. Diarrhea and arthralgia were classified as grade 2 toxicity in their most severe forms (Walter et al. Blood. 2016;127(4):411–9. https://doi.org/10.1182/blood-2015-08-664,086. Epub 2015 Nov 5).

15.2.1.3 Acalabrutinib and BGB-3111

Several other inhibitors of BTK are also in development. Acalabrutinib is a covalent inhibitor of BTK with a more selective profile than ibrutinib. A phase I study of acalabrutinib in relapsed chronic lymphocytic leukemia (CLL) demonstrated a response rate of 95% when the drug was given twice daily. The most common side effects reported included headache and diarrhea [10]. Studies are ongoing with acalabrutinib as a single agent and in combination with chemotherapy in patients with untreated and relapsed DLBCL. BGB-3111 is another specific, irreversible inhibitor of BTK. Preclinical studies suggest greater selectivity for BTK versus other TEC- and EGFR-family kinases compared to ibrutinib [11]. Phase Ib studies of BGB-3111 in 46 patients with aggressive lymphomas, including mantle cell lymphoma, demonstrated an overall response rate of 61% to the drug as a single agent. Frequent side effects included bruising, changes in bowel habits, fatigue, and upper respiratory tract infections [12]. How the activity of next-generation BTK inhibitors compare to ibrutinib in aggressive lymphoma will require further study.

15.2.2 SYK Inhibitors

The cytoplasmic non-receptor tyrosine kinase, SYK, is constitutively activated in B-cell lymphomas and plays a critical role in BCR signaling. SYK amplification of the BCR signal promotes subsequent downstream signaling through BTK and PI3K, and the kinase has been shown to act as an oncogene in certain hematologic malignancies [13]. Several SYK inhibitors are currently in clinical trials for hematologic malignancies including fostamatinib, entospletinib, cerdulatinib, and TAK-659.

15.2.2.1 Fostamatinib

Fostamatinib was one of the first oral SYK inhibitors to enter into clinical studies for lymphoma. In a pilot phase I/II study of 22 patients with refractory DLBCL, the overall response rate was 22% with a median progression-free survival of 2.7 months. Side effects of the drug included diarrhea, neutropenia, and thrombocytopenia [14]. Unfortunately, larger phase II studies at various doses demonstrated minimal activity in aggressive lymphoma (overall response rate of 3%) with similar adverse events [15]. Responses also did not appear to differ regardless of cell of origin.

15.2.2.2 Entospletinib

Entospletinib (GS-9973) is another orally available selective inhibitor of SYK. The agent has shown promising activity in relapsed and refractory CLL with up to 61% of patients demonstrating response [16]. In pretreated indolent lymphoma, approximately 13% of patients responded to the drug. Common adverse events associated with the drug included dyspnea, pneumonia, neutropenia, transaminitis, and fever [16]. Although clinical data is lacking in DLBCL, preclinical models in aggressive hematologic malignancies including a DLBCL cell lines suggest SYK inhibition can lead to cell cycle arrest and apoptosis by preventing SYK-dependent activation of PLCγ2 and AKT [17]. Combination studies with the PI3K inhibitor idelalisib and entospletinib in relapsed NHL and CLL were halted due to unexpected and often severe immune toxicities [18].

15.2.2.3 Cerdulatinib

Cerdulatinib (PRT062070) is a dual JAK/SYK total inhibitor which has shown promising activity in CLL and in preclinical models of large cell lymphoma. In ABC and GCB cell lines, cerdulatinib induced cell death associated with caspase-3 cleavage [19]. Phase I studies with cerdulatinib in relapsed CLL, indolent lymphoma, and DLBCL are underway with interim results demonstrating tolerable safety profiles [20].

15.3 PI3K/mTOR/AKT Pathway

The phosphoinositide 3-kinases (PI3Ks) play a pivotal role in multiple cellular processes, including cell differentiation, proliferation, cell cycle, cellular metabolism, angiogenesis, survival, apoptosis, and motility [21]. PI3Ks are intracellular lipid kinases that transmit extracellular signals from transmembrane receptors such as G-protein-coupled receptors (GPCRs) and receptor tyrosine kinases (RTKs) to the cytoplasm and thereby regulate key cellular processes [22]. Downstream effectors of PI3K signaling include the AKT/mTOR pathway, which governs oncogenic processes such as metabolism, chemoresistance, cell cycle regulation, growth, and proliferation [23, 24]. The PI3K/AKT/mTOR pathway is deregulated in a subset of cases in a variety of lymphoma subtypes including Hodgkin, diffuse large B-cell, mantle cell, and follicular lymphoma [25–28].

15.3.1 PI3K Inhibitors

Class I PI3Ks are heterodimers consisting of regulatory (p85) and catalytic (p110) subunits. The p110 subunit exists as four isoforms (α, β, γ, δ) with nonoverlapping functions and different expression profiles. The α and β isoforms are expressed ubiquitously, while the γ and δ isoforms are expressed primarily in the hematopoietic tissues. Knockout studies in mice have shown that lack of p110c and p110d is associated with an impaired immune response and B-cell development [29]. Due to its prominent role in lymphoma, there is great interest in the development of PI3K inhibitors in clinical trials.

15.3.1.1 Idelalisib

Idelalisib is a PI3K delta inhibitor and has been extensively studied in indolent lymphoma [30, 31] but not significantly in DLBCL. In mantel cell lymphoma, a phase I trial investigated idelalisib as a single agent in 40 patients with a median of four prior therapies [32]. The ORR was 40% including two patients who attained complete remission (CR). Despite promising response rates, single agent therapy rarely resulted in durable remissions, prompting subsequent combination studies. A separate phase I study combines idelalisib with everolimus or bortezomib or rituximab and bendamustine, with a response rate of 46% [33]. Other combination studies with idelalisib and BTK inhibitors are currently under investigation in patients with B-cell malignancies including non-GC DLBCL. Regarding toxicity, elevation of liver transaminase is frequently observed as well as the class-specific side effect diarrhea (reported in approximately 25% of patients). Neutropenia has also been reported and occurs in a dose-independent manner. Pneumonitis was seen in 3% of patients treated on single agent studies and generally occurred after several months of treatment [33].

15.3.1.2 Duvelisib

Duvelisib is an oral, dual inhibitor of the PI3K delta and gamma isoforms which is also being investigated in lymphoid diseases. In a phase I trial, including relapsed/refractory NHL patients, duvelisib has demonstrated clinical activity and a safety profile similar to idelalisib [34, 35]. Although the maximum tolerated dose was 75 mg BID, concurrent pharmacokinetic (PK) studies suggested full target inhibition at lower doses, and 25 mg BID was selected for further testing. The 26 patients with aggressive B-cell NHL who enrolled in the phase I study achieved an ORR of 19% (8% CR). The overall response rate was 50% in MCL (5/10 including 1 CR), 50% in peripheral T-cell lymphoma—including 3 CR out of 16 patients—and 32% in cutaneous T-cell

lymphoma. Severe adverse events (≥ 3) occurred in 84% of patients, mainly neutropenia, thrombocytopenia, and transamanitis [35].

15.3.1.3 Copanlisib

Copanlisib is a novel dual inhibitor of PI3K delta and gamma isoforms. In preclinical models, copanlisib was predominantly active in ABC DLBCL [36]. A phase II study by Lenz and colleagues evaluated copanlisib in 67 patients with relapsed or refractory DLBCL and three or more prior therapies. The overall response rate was 25% with a median of PFS of 8.1 months in responders. The main adverse events included hypertension and hyperglycemia. Twenty-five percent of patients with ABC DLBCL achieved a complete remission [37]. Another phase II trial evaluated copanlisib in 33 patients with indolent lymphoma and 51 with aggressive lymphoma, mostly T-cell lymphoma. The overall response rate was 27% in the aggressive cohort with a PFS of 70 days. Similar adverse events were observed. Interestingly, a predominant activity was observed in tumors with up-regulation of PI3K pathway [38].

15.3.1.4 Umbralisib

Umbralisib (TGR-1202) is a potent and selective inhibitor of p110δ, with a unique molecular structure. Umbralisib has been shown to induce cytotoxicity, and inhibit AKT phosphorylation at submicromolar concentrations in cell lines regardless of 17p deletion, and was equipotent to idelalisib [39]. TGR-1202 has shown promising activity in patients, with a 94% nodal response rate observed in CLL patients treated with umbralisib monotherapy. Preliminary results suggest that hepatotoxicity, colitis, and opportunistic infections, such as pneumonia and pneumonitis, were less common, possibly due to conservation of Th2 cytokine expression and GATA-3 mRNA compared to other PI3Kδ inhibitors as well as a differential effect on regulatory T cells [40]. To date, little data has been reported with umbralisib as a single agent in DLBCL. O'Connor and colleagues reported responses in 3 out of 12 patients from a single agent monotherapy study [41]. A subsequent combination trial with anti-CD20 therapy reported partial remissions in 4 out of 12 patients with DLBCL [42]. Larger studies are underway in DLBCL, stratifying patients according to cell of origin (GCB/ABC).

15.3.2 mTOR Inhibitors

The mechanistic target of rapamycin (mTOR) is a core component of mTOR complex 1 and mTOR complex 2, which regulates different cellular processes such as cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription. The most established mTOR inhibitors are called rapalogs (rapamycin and its analogs).

15.3.2.1 Temsirolimus

Temsirolimus has significant activity in relapsed mantle cell lymphoma. Single agent studies have shown response rates of 38% or combined with rituximab (ORR of 59%) [43]. Based on these trials, temsirolimus has received orphan drug approval for relapsed mantle cell lymphoma in Europe. Early studies also suggest temsirolimus has efficacy in other NHL subtypes, including DLBCL [44].

15.3.2.2 Everolimus

Everolimus is an oral mTORC1 inhibitor that is approved by the Food and Drug Administration for relapsed renal cell, brain, neuroendocrine, and hormone receptor-positive breast cancers. A phase II trial of everolimus in relapsed aggressive lymphoma demonstrated an ORR of 30% [45]. Everolimus was also evaluated in combination with the histone deacetylase inhibitor panobinostat in relapsed or refractory lymphomas. Toxicities were mild, and the ORR was 33% with complete response rate of 15% in heavily pretreated lymphoma. The limiting dose toxicity was thrombocytopenia [46]. Unfortunately, in a subsequent a phase III trial, adjuvant everolimus in patients with poor-risk DLBCL demonstrated no improvement in disease-free survival [47]. A newer generation of mTOR inhibitors, which are now entering clinical trials, is able to block

mTORC1 and mTORC2 and might allow greater efficacy and avoidance of the compensatory phosphorylation of AKT.

15.3.3 AKT Inhibitors

Perifosine is a first-generation AKT inhibitor that functions via inhibition of AKT translocation to the cell membrane. Combined in a phase II trial, sorafenib and perifosine had an ORR of 22% in relapsed or refractory lymphoproliferative diseases [48]. Due to limited efficacy and moderate toxicities, there are currently no ongoing clinical trials evaluating perifosine in patients with lymphoma.

A second-generation AKT inhibitor, MK-2206, was tested in a phase II trial including 59 patients with relapsed or refractory lymphoma. The ORR was 14% including two CR and six PR, with a median duration of response of 5.8 months [49].

15.4 Anaplastic Lymphoma Kinase Inhibitors

15.4.1 Role in T-cell and B-cell lymphomas

Chromosomal translocation t(2;5) is associated with approximately 60% of anaplastic large cell lymphomas (ALCLs). The translocation creates a fusion gene consisting of the anaplastic lymphoma kinase (ALK) gene and the nucleophosmin (NPM) gene. The product of the NPM-ALK fusion gene is oncogenic. In other cases, ALK is fused to TPM3 or more rarely to other partners, such as TFG, ATIC, CLTC1, TPM4, MSN, ALO17, and MYH9 [50]. ALK-positive DLBCL is a rare variant of DLBCL. In a retrospective cohort of 38 cases of ALK-positive DLBCL, most patients had an aggressive clinical course with advanced stage at diagnosis and poor outcome. Overall survival was 20.3 months in this CHOP and CHOP-like regimen-treated cohort [51].

15.4.2 Overview of Active Studies

Limited data exists utilizing ALK inhibitors in lymphoma. In a retrospective cohort of 11 patients with relapsed ALK-positive ALCLs treated with the ALK inhibitor, ceritinib, the overall response rate was 90%, with seven patients in durable CR. OS and PFS at 2 years were 72.7% and 63.7%, respectively [52]. Safety and tolerability of ceritinib were evaluated in a phase I trial enrolling 304 patients with ALK-positive tumors, among which three had relapsed ALK-positive ALCL. Two of them achieved a durable CR and one a PR [53]. Given the high remission rate, long duration of remission, and acceptable tolerability of treatment, ALK inhibitors may have promise in the treatment of patients with ALK-positive ALCL. Phase II studies are ongoing to evaluate the activity of ceritinib as single agent in patients affected by resistant or refractory ALK-positive lymphoma.

15.5 Aurora Kinase Inhibitors

The aurora family of kinases regulate key cell cycle events including mitotic processes such as chromosome alignment and segregation. Overexpression of aurora kinases has been observed in several malignancies including aggressive lymphomas, and efforts have been made recently to develop agents targeting members of the kinase family. Preclinical studies suggest that inhibition of aurora kinases can result in mitotic arrest, chromosome misalignment, and apoptosis [54].

15.5.1 Alisertib

Alisertib (MLN8237) is an orally available selective aurora A kinase inhibitor with antiproliferative activity across several human tumor cell lines [54]. The agent has also been shown to inhibit tumor growth in mouse xenograft models with DLBCL [55]. Initial phase I studies

in relapsed myeloma, non-Hodgkin's lymphoma, and CLL were recently reported. Responses were observed and 13% of patients with 2 out of 17 patients with DLBCL attaining partial remission. The drug was associated with revisable neutropenia, thrombocytopenia, and leukopenia [56].

Friedberg and colleagues reported a subsequent phase II study of alisertib in aggressive B- and T-cell non-Hodgkin's lymphomas. Forty-eight patients were enrolled, including 21 patients with relapsed DLBCL. Although the drug was well tolerated, only 3 out of 21 patients (14%) with DLBCL responded [57]. Single agent and combination studies of alisertib in aggressive B-cell and T-cell lymphoma are ongoing.

15.6 Conclusion

With improved understanding of key cellular pathways and their respective kinase drivers, more therapeutic targets in DLBCL are emerging. Unfortunately, most studies targeting single kinases in aggressive lymphoma have been met with low response rates and short remissions. Toxicity modeling has also been challenging due to several inhibitors' lack of specificity and the ubiquitous nature of many kinase targets. Next-generation agents and studies will focus on gaining a deeper understanding of not only the effect of target inhibition on both malignant and normal cells but developing predictive biomarkers for efficacy and toxicity.

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