

New drugs for the treatment of non-Hodgkin lymphomas

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Abstract: Non-Hodgkin lymphomas (NHL) are diverse diseases either of mature B-cell or T-cell derivation. Despite being generally chemosensitive diseases, the last decade has focused on developing more targeted agents based on improved insights of underlying biology. The hope is that more targeted and biologically rational treatments will improve both the efficacy and toxicity profile of standard approaches, with the ultimate goal of improving clinical outcomes. Among the newest agents to be approved are inhibitors of B-cell receptor (BCR) and PI3K signaling; however, a number of other classes of agents such as selective inhibitors of nuclear export (SINE), inhibitors of immune regulation such as PD1 inhibitors, and small molecule inhibitors of apoptosis are on the horizon. In addition, growing clinical evidence supports continued and new applications for immunomodulatory agents, proteasome inhibitors and histone deacetylase inhibitors. Altogether, this is an exciting time for NHL, with a number of promising agents and early clinical data. The key path forward will be to better apply these new agents in a personalized way, which will hopefully constitute the next generation of trials.

Keywords: B-cell receptor (BCR) inhibitors; lymphoma; clinical trials; targeted agents

Submitted Nov 29, 2014. Accepted for publication Jan 30, 2015.

doi: 10.3978/j.issn.2304-3865.2015.03.01

View this article at: <http://dx.doi.org/10.3978/j.issn.2304-3865.2015.03.01>

Introduction

Drug development in cancer, especially lymphomas, has undergone major shifts over the past decade. Despite the success and continued use of combination chemotherapy for many patients, there is a concerted drive to replace cytotoxic agents with more targeted drugs that capitalize on pathways and biologic processes that are specifically relevant in lymphomas. While monoclonal antibodies were the first wave of targeted therapeutics, there are now an ever-increasing generation of oral and/or biologic agents that capitalize on improved understanding of lymphoma pathogenesis. This review will address some of the newer, non-monoclonal antibody agents, with a focus on those that are either already approved for clinical use or with strong emerging data or significant clinical potential.

Inhibition of B-cell receptor (BCR) signaling

All human cancers, including lymphomas, derive from

previously normal cells that undergo transformation to a malignant state. Although transformed neoplastic cells retain some features of their non-malignant counterpart, they become increasingly reliant on a variety of survival mechanisms. Perhaps the best example of a normal survival pathway co-opted by lymphoma cells is the BCR and its downstream signaling components. The BCR, or surface immunoglobulin, is a protein complex on the surface of all mature B-cells and delivers cell survival signals via either tonic or triggered mechanisms (1). A number of kinases proximal to the cytoplasmic aspect of the BCR are critical to BCR signaling, and many of them have increased expression and activity as reflected by gene-expression profiling and other methodologies. Among the most important mediators of BCR function are spleen tyrosine kinase (SYK), LYN, Bruton's tyrosine kinase (BTK), CD79a and CD79b, and PI3K. A number of agents target these kinases, but the two that are furthest along are the BTK inhibitor, ibrutinib, and the PI3K δ inhibitor, idelalisib. Both of these agents are recently approved for use by the FDA based on exciting

single agent and emerging combination data.

BTK inhibitors

BTK is a Tec (tyrosine protein kinase) family kinase that is congenitally absent in X-linked Bruton's agammaglobulinemia, and leads to a clinical phenotype of absent B-cells and absent immunoglobulins (2). Ibrutinib, now approved in The United States for use in chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), was designed as a specific and potent oral inhibitor of BTK. A multicenter phase I trial evaluated two schedules and multiple dose levels across a variety of lymphoid malignancies and found an overall response rate of 60% in heavily pretreated patients (3). No maximum tolerated dose was established, and the trial was halted several dose levels beyond maximal binding of ibrutinib to BTK as reflected by a unique pharmacodynamics assay. Activity was seen in multiple dose levels and schedules, but the 560 mg per day (NHL) and the 840 mg per day (CLL) doses were initially taken forward for further study.

Ibrutinib is highly active in CLL; a pivotal multicenter phase II single agent study in 85 relapsed/refractory patients showed an overall response rate of 71% (4). Patients in this study were heavily pretreated, with a median of four prior regimens (range, 1-12) and near-universal prior nucleoside analog therapy, rituximab therapy and half of patients having either 17p13.1 or 11q22.3 deletion. While the high response rate is impressive, the progression-free survival (PFS) of 75% at 26 months underscores the activity and prolonged benefit in patients with few other options. Importantly, even patients with the most adverse genetic features, including deletion of 17p13.1, respond to ibrutinib. Given the chemoresistance and lack of standard options for patients with 17p13.1, ibrutinib is now also approved for front-line use specifically in this population. Further solidifying ibrutinib's role are the final results of the randomized RESONATE trial, which showed significant improvement in both progression-free and overall survival (OS) for relapsed/refractory CLL patients treated with ibrutinib as compared to ofatumumab (5).

A recurrent phenomenon in CLL patients is a brisk and often prolonged lymphocytosis that should not be confused with progression. The lymphocyte count can increase dramatically, but often occurs with improvement in other hematologic parameters and likely reflects a compartment shift from lymph nodes and bone marrow to the peripheral blood. It is important to recognize the treatment-related

lymphocytosis and understand that resolution may take many months. Of note, activity in several of these trials did not differ at several of the tested doses and 420 mg per day is the current approved dose in CLL.

Ibrutinib also has strong single agent activity in relapsed and refractory MCL. MCL is an uncommon lymphoma subtype, characterized by being both incurable and relatively aggressive, particularly in relapsed and refractory settings. A large phase II trial of 111 heavily pretreated MCL patients with single agent ibrutinib 560 mg per day found a response rate of 68% (complete response rate 21%), far exceeding any other single agent in this setting (6). The responses were durable, with median response duration of 17.5 months and median OS not reached with 15 months of follow up. The authors of this paper reported that responses increased with continued dosing. Although uncommon, a unique toxicity with ibrutinib is increased grade 1 and 2 bleeding in 17% of pts, and serious bleeding including subdural hematomas in four MCL patients. This risk of bleeding occurred mainly in patients on concurrent therapeutic anticoagulation with warfarin; however, the increased bleeding risk warrants holding ibrutinib prior to invasive procedures and guidance for perioperative management is included in the FDA label.

A third lymphoma subtype in which ibrutinib may have an important role is the activated B-cell (ABC) subtype of diffuse large B-cell lymphoma (DLBCL). Over a decade ago, gene expression profiling studies established two molecular subtypes of DLBCL: germinal center (GC) and activated B-cell (ABC, also called non-GC) subtypes, based on similarities to normal B-cell counterparts (7). The clinical significance of this "cell-of-origin" (COO) distinction is that GC-DLBCL has superior outcomes compared to non-GC-DLBCL, which has been validated in both CHOP and R-CHOP treated patients. The underlying pathogenesis of these two subtypes of DLBCL are unique, with non-GC-DLBCL now shown to utilize BCR-signaling as a major survival mechanism (8). Indirect support that BCR signaling is more important in non-GC-DLBCL comes from clinical observations that ibrutinib induced responses in 40% of non-GC-DLBCL as compared to only one partial response among 35 GC-DLBCL (9). This study is ongoing but has already prompted large scale investigations exclusively in non-GC-DLBCL.

Ibrutinib's role in other lymphoid malignancies remains to be established. Despite encouraging activity in follicular lymphoma (FL) in the initial phase I study, a subsequent phase II (NCI9271) trial found a modest response rate of

30% among 40 patients with relapsed/refractory FL (10). Of interest, response was higher in rituximab-sensitive as compared to rituximab-refractory patients; the explanation for this observation is unknown. In contrast, single agent ibrutinib appears highly active in relapsed lymphoplasmacytic lymphoma with an overall response rate of 80% and suggestion that mutations in CXCR4 may impact drug sensitivity (11).

PI3K inhibitors

Further downstream of BTK is PI3K. PI3K belongs to a ubiquitous and highly conserved family of kinases with tissue-specific isoforms (alpha, beta, gamma and delta) (12). The delta isoform is specifically expressed in hematopoietic cells, and is thus a target of interest. In normal cells, PI3K is both upstream and downstream of a number of important pathways that collectively regulate metabolism, growth, proliferation. Notable downstream targets include Akt, mTOR, and NFκB signaling (13). However, the main impact of PI3Kδ inhibition seems to be blockade of BCR signaling. Idelalisib (formerly CAL-101, GS-1101) is a highly specific and potent inhibitor of the delta isoform of PI3K, and is now FDA-approved for use in refractory indolent lymphoma and in CLL in The United States.

Idelalisib has substantial single agent activity in CLL, and appears synergistic with rituximab. A multicenter dose escalation study in 54 heavily pretreated CLL patients, including over 90% with unmutated phenotype and 70% with treatment-refractory disease, established single agent activity with a response rate of 72% and median PFS of nearly 16 months (14). Of interest, lymphocytosis, similar to BTK-blockade, is a common observation and should not be confused with progression in patients who otherwise have improved cytopenias, symptoms or lymph node burden. A separate randomized phase III placebo-controlled trial of rituximab with or without idelalisib in relapsed CLL showed superior response, PFS and OS in patients receiving the combination (15). The improvement in OS (92% for the combination versus 80% for rituximab alone, HR =0.28 with P=0.02) prompted early closure of the study, and established this combination as an option for patients with relapsed CLL.

Idelalisib also has clinical activity across a range of indolent lymphomas. A large phase I trial with eight dose levels evaluated safety and toxicity of single agent idelalisib in patients with relapsed and refractory indolent lymphomas and reported an overall response rate of 47% with median

response duration of over 18 months (16). A subsequent phase II trial evaluated 150 mg twice daily in patients who were required to either relapse within six months of both rituximab and alkylating agents, or be refractory to these agents. In this population of heavily pretreated patients (median of four prior therapies), idelalisib had a response rate of 57% and median duration of response of almost one year (17). Importantly, each of these trials identified some unique toxicities associated with idelalisib therapy. While the most common adverse effects are diarrhea, nausea, fatigue and rash, there is also an unexplained transaminase elevation and delayed colitis. Many patients were able to resume idelalisib at a lower dose following resolution of the hepatotoxicity.

The activity of idelalisib in MCL seems more modest (18). Among 40 patients with relapsed/refractory disease, the overall response rate was 40% with rare complete responses, and short median response durations of less than three months. However, patients were very heavily pretreated, including having received a median of four prior therapies and 43% being refractory to their most recent treatment. The relatively decreased activity may also be related to an increased role of mTOR and AKT in MCL pathogenesis, which are both downstream of PI3K signaling.

One important mechanism of resistance to idelalisib may be the redundant PI3K family members, and some groups have proposed that increased gamma isoform of PI3K can compensate for delta isoform blockade. IPI-145 is an oral dual inhibitor of both the delta and the gamma isoform, and is currently in active investigation. Preliminary data suggest activity across a range of both B and T-cell histologies. Flinn and colleagues report an overall response rate of 65% in heavily pretreated indolent B-cell lymphomas, while Horwitz and colleagues observed responses in 47% of peripheral T-cell lymphoma patients (19,20). Toxicity was overall manageable, with the most common adverse effects being transient transaminase elevation and neutropenia; early reports of increased opportunistic infections are addressed by including prophylaxis in these heavily pretreated patients.

Other BCR signaling inhibitors

There are several other components of BCR signaling that are potential targets, including LYN and SYK. These compounds, while interesting, have not moved forward at the pace of either ibrutinib or idelalisib. Fostamatinib disodium is an oral agent that is highly specific for SYK. A phase I trial identified neutropenia, diarrhea and thrombocytopenia as the dose-limiting toxicities. Among 68

heavily pretreated lymphoma patients included in the phase 2 portion, the overall response rate varied by histology and ranged from 10% in FL patients to 55% in CLL patients. Dasatinib (BMS-354825) is an oral kinase inhibitor that is much less specific than fostamatinib, and inhibits several kinase families including BCR-ABL, SRC, c-KIT, PDGF receptors and ephrin (EPH) receptor kinases. Approximately one-third of heavily pretreated B- and T-cell lymphoma patients responded in a small early phase trial (21). The major toxicities included myelosuppression and pleural effusions.

An important aspect of several of these kinases is that they are active not only as part of BCR signaling, but also are independently active in T-cell malignancies and Hodgkin lymphomas which clearly would not express the BCR. As an example, ITK (interleukin-2-Inducible T-cell kinase), similar to BTK, is a Tec family kinase. ITK appears to be a substrate for ibrutinib and can skew T-cell subsets (22). While early, these observations provide rationale for broader testing of kinases both related to BCR activation and otherwise.

Immunomodulatory agents (IMiD)

In contrast to the concept that the above-mentioned small molecule inhibitors and kinase inhibitors have well-defined targets and known mechanisms of action, another genre of agents active in lymphomas are the immunomodulatory drugs such as thalidomide, lenalidomide and pomalidomide which have broad effects on both the malignant and non-malignant cells in lymphoid cancers. Thalidomide is the prototype of IMiD's but was found to be too toxic and with relatively low efficacy (23). Lenalidomide was designed to reduce the sedation and neurologic toxicity associated with thalidomide, but has its own set of adverse effects as discussed below. Pomalidomide is just entering trials in lymphoma, and therefore most of the clinical data involves lenalidomide. The precise mechanism of action of IMiDs is unknown, but these agents have pleiotropic effects in cancer cells that may vary amongst malignancies. These effects include decreased IL-6, VEGF, TNF alpha (24). In multiple myeloma, a protein of unknown function, called cereblon, is the putative target of lenalidomide (25). However, this has not been evaluated in lymphomas where lenalidomide has been shown to skew the T-cell receptor repertoire, decrease IL-6 and TNF- α , and shift polarization in CLL cells that may facilitate recognition by the immune system (26). One proposed concept is that these effects not only exert direct cytotoxicity against lymphoid malignancies, but also impact

the cells constituting the microenvironment supporting lymphoma cell survival.

Lenalidomide has single agent activity in several lymphomas. The NHL-003 trial was a phase II trial testing lenalidomide (25 mg daily on days 1-21, repeated every 28 days) in 217 patients with several types of relapsed lymphomas (27). There was broad activity, including 28% ORR in DLBCL, 42% ORR in both MCL and FL grade 3, and 45% ORR in transformed lymphomas. Lenalidomide monotherapy has particular activity in MCL where subset analysis of the NHL-003 trial and the pivotal MCL-001 (EMERGE) trial demonstrated responses in approximately one-third of patients (28,29). An update of the NHL-003 trial showed that among 57 heavily pretreated MCL patients, the overall response rate was 35% (29). While the median PFS was 8.8 months, the duration of response was dependent on the quality of response, and the median duration of response was not reached for CR/CRu patients with a follow up time of nearly three years. The median DR for all responders was 23 months. Similarly, the EMERGE trial, which led to the approval of lenalidomide for relapsed/refractory MCL in 2013, demonstrated an ORR of 28% in 134 elderly patients (63% of patients were over age 65 years) (28). Similar to other trials, the median PFS was relatively short at 4 months, but the median DR among responders was over 16 months. The discrepancy between the PFS and DR suggests that there is a subset of patients deriving significant benefit from lenalidomide, whereas the activity is more limited in others. Developing predictive factors for response is critical for optimal use of lenalidomide, but has been elusive to date.

An extension of subtype-specific activity with lenalidomide can be seen in DLBCL where there is emerging observation of a differential response between GC versus non-GC subsets. The importance of cell-of-origin (COO) in DLBCL has been established in both CHOP and R-CHOP series, with non-GC patients having an inferior outcome (7,30). As mentioned above, lenalidomide has modest activity in DLBCL reflected in the NHL-003 trial with a 28% ORR but a very short PFS of only 2.7 months (27). However, a separate study of 40 relapsed/refractory patients found that there was a significant difference in clinical response rates (ORR 8.7% *vs.* 52.9%, $P=0.006$) and median PFS (1.7 *vs.* 6.2 months, $P=0.004$) for GC-DLBCL and non-GC-DLBCL, respectively (31). While retrospective, these differences are compelling and have prompted evaluation of COO in frontline DLBCL studies in which lenalidomide has been added to R-CHOP (32,33). In these trials, the negative

prognostic significance of COO seems abrogated by the addition of lenalidomide such that PFS and even OS of non-GC DLBCL matches the outcomes of GC-DLBCL. These studies are intriguing and ongoing prospective studies should help clarify the impact of lenalidomide in non-GC DLBCL.

Lenalidomide appears particularly active when combined with rituximab, with some studies suggesting a synergistic (and not simply additive) effect. For example, lenalidomide has a 27% response rate in relapsed/refractory FL (34). When combined with rituximab, the CALGB/ALLIANCE found a response rate of 75%, including over 30% complete responses (35), which seems more than additive. Given these results, combination lenalidomide and rituximab (dubbed R-squared, or R2) has been tested in treatment-naïve FL by several groups. In the frontline setting, the CALGB/ALLIANCE showed a response rate of 93% (53/57); the CR rate was 72% (36). There was no significant association between CR rate and FLIPI risk, histological grade, or bulky disease. Fowler and colleagues similarly showed a response rate of 98% and CR rate of 87% in treatment-naïve FL again found activity independent of tumor bulk, tumor burden (reflected by GELF criteria), and FLIPI score (37). These promising data have led to the international RELEVANCE trial which directly tests R2 against chemoimmunotherapy; this trial has reached its accrual goal with results expected shortly.

Proteasome inhibitors

While not entirely new, proteasome inhibitors retain an important role in lymphoma management, with a number of combination trials recently presented. As a single agent, bortezomib has established activity in MCL and is approved in the US for this indication. The PINNACLE study tested bortezomib 1.3 mg/m² on days 1, 4, 8 and 11 of a 21-day cycle in patients with relapsed and refractory MCL; among 141 assessable patients, the overall response rate was 33% with a median duration of response 9.2 months and median time to progression of 6.2 months (38). Given the promising activity in relapsed MCL, bortezomib has been tested as part of combination regimens in non-transplant eligible treatment-naïve MCL (39,40). A European group tested bortezomib as a replacement for vincristine in the R-CHOP regimen, with preliminary results recently reported (39). This study, LYM-3002, was a randomized multi-center phase 3 trial comparing standard R-CHOP (n=244) versus VR-CAP (n=243) in which bortezomib replaces vincristine. Patients were treated with 6-8 cycles

and PFS by an independent radiology review committee was the primary endpoint. The VR-CAP regimen had superior PFS (24.7 *vs.* 14.4 months, *P*<0.001) and significantly improved outcomes for all secondary endpoints including time to progression, median time to next therapy, and median treatment-free interval. With a median follow up of 40 months, there was no statistical difference in OS. There was more thrombocytopenia and neutropenia in the bortezomib-arm but no difference in peripheral neuropathy. Based on the improved efficacy, the authors propose VR-CAP as an acceptable option. A US Intergroup study is testing bortezomib with bendamustine and rituximab in the frontline setting.

Bortezomib is also active in other lymphomas, with single agent response rates of 50% in small studies of relapsed and refractory FL (41). Incorporation of bortezomib into front-line combinations is feasible, although the additive benefit is modest. For example, a large phase III trial of bortezomib and rituximab versus rituximab alone showed a statistically significant improvement in PFS, but the absolute improvement was only four months which was not considered clinically meaningful (42). Bortezomib was also added to bendamustine and rituximab in an open-label phase II trial (43) with encouraging results. Overall, bortezomib is an active agent in FL although its role remains undefined.

Perhaps the most biologically dependent entity related to the proteasome pathway is the non-GC derived subtype of DLBCL (30). With this rationale in mind, several investigators have combined bortezomib and R-CHOP chemotherapy (44) and observed, in a small set of patients, that outcomes for non-GC DLBCL were similar to GC-DLBCL. This observation suggests that the addition of bortezomib to R-CHOP may overcome the negative prognostic significance of non-GC subtype. There is currently an ongoing phase III trial comparing R-CHOP with and without bortezomib in DLBCL.

The limiting toxicity with bortezomib is peripheral neuropathy which is delayed in onset, but often very prolonged and debilitating. Subcutaneous formulations may improve the risk profile of this agent, and several studies suggest similar efficacy with decreased toxicity. In addition, second and third generation proteasome inhibitors in development may offer a more favorable toxicity profile.

Selective inhibitors of nuclear export (SINE) agents

There are a number of ways that cells control and regulate protein function. Inhibition of protein degradation, such

as proteasome inhibitors discussed above, is one such mechanism. However, it is also increasingly clear that both normal and malignant cells have evolved means of actively controlling the transport of key mRNA transcripts and proteins between the nucleus and the cytoplasm. Proteins termed importins and exportins function as transporters and control this passageway. SINE prevent efflux of important mRNA and proteins (45). The agent furthest along in this category is selinexor (KPT-330), a covalent XPO-1/CRM-1 inhibitor. XPO-1, or exportin 1, is the only known nuclear exporter of most tumor suppressor proteins. Its levels are significantly elevated in several lymphoid malignancies and is associated with a pro-survival cancer phenotype. Selinexor has been shown to decrease many proto-oncogenes including MYC, BCL2, BCL6, BTK, and Cyclin D; in addition, selinexor treatment is associated with increased I κ B and subsequent inhibition of NF- κ B, which has been shown to affect levels of p-ERK, surviving, p53, MYC and in pre-clinical models (46).

An early phase clinical trial in a broad collection of lymphoma subtypes was presented at ASCO 2014 (47). In this phase I study, 51 patients with relapsed/refractory lymphomas (including T-cell phenotypes) were treated with selinexor 3-70 mg/m² on a variety of schedules. The most frequent toxicities were nausea, anorexia and fatigue. Although grade 3 and 4 cytopenias were common, this is more reflective of the eligibility criteria which allowed an absolute neutrophil count of 1,000/ μ L and platelet threshold of 30,000/ μ L. There is encouraging early activity with an overall response rate of 29% and disease control (defined as partial and complete response plus stable disease) in 74% of patients, including most patients with DLBCL and Richter's transformation. While very early, these observations have prompted a number of ongoing single agent and combination studies, some of which include dexamethasone to counter the asthenia.

Programmed death 1 (PD-1) and programmed death ligand (PDL-1 and PDL2) inhibitors

Consistent with the observation of micro-environmental impact on lymphoma outcome, there is increasing evidence that the immune system "permits" lymphoma survival. The relationship between immune tolerance and malignant cell survival in lymphoma is elegantly reviewed elsewhere (48), and it is clear that there are number of important mechanisms of interaction with the immune system. One increasingly appreciated component of malignant B-cell survival is

induction of T-cell tolerance via PD1-PD1L interactions. Normally, antigen-presenting cells (APC) present antigen in the context of major histocompatibility complex (MHC) to T-cells, leading to an effective immune response. In order to prevent excessive immune-mediated toxicity, there is a balancing system by which PD1L on APC's dampen the response by binding to PD1 receptor on T-cells. Lymphoma cells, among other malignant and virally transformed cells (49), have increased expression of PDL1 which is an independent negative prognostic marker correlated with an aggressive course. The increased PDL1 expression suppresses the T-cell response, effectively leading to immune tolerance to the malignant lymphoma. Inhibitors of this interaction have been very exciting in solid tumors, and their potential in lymphomas is being evaluated through a growing number of clinical trials.

There are several PD1 inhibitors being tested in hematologic malignancies, including pidilizumab (CT-011), pembrolizumab (MK-3475), nivolumab (BMS936558) and others earlier in development [reviewed in (50)]. PD1 blockade seems most promising in relapsed/refractory Hodgkin lymphoma, with several abstracts recently presented. Moskowitz and colleagues found a response rate over 50% in heavily pretreated cHL patients, including 67% failing a prior autologous stem cell transplant and all having disease progression after brentuximab vedotin (51). Similarly, nivolumab showed an overall response rate of 87% among 23 heavily pretreated patients and independent of prior brentuximab vedotin exposure; early follow-up data shows 86% PFS at 24 weeks (52). PD1 blockade may also be important across a range of lymphoid malignancies as reflected by a phase II trial of nivolumab showing responses in DLBCL, FL, and T-NHL (53). An interesting phase II trial evaluated pidilizumab every 42 days for three cycles in the post-autologous stem cell transplant (ASCT) setting in DLBCL patients (54). This trial met its pre-specified endpoint of improving PFS compared to historical controls in a group of 66 evaluable patients; despite having a number of high-risk patients, the 16-month PFS was 72%. A phase II combination trial with rituximab in relapsed and refractory FL also showed activity with 66% of 29 evaluable patients responding. Again, there were no significant adverse safety signals. Given the unique mechanism of action and strong potential ability to develop combinations, PD1 inhibitors are very promising and a number of trials are underway.

Inhibition of apoptosis

One of the most fundamental oncogenic strategies is a

cancer cell's ability to evade apoptosis. Although there are a number of anti-apoptotic proteins, the most ubiquitous finding in lymphoid malignancies is overexpression of BCL2 and its family members, which confer a drug resistant phenotype. However, targeting BCL2 has been challenging, in large part due to the complex and highly redundant family of BCL2-associated proteins. BCL2 has been considered to be the key target, but early agents against BCL2 had only modest activity. Currently, the most promising agents do not directly inhibit BCL2, but instead function as "mimics" of the pro-apoptotic naturally occurring BH3-only proteins. BH3-only proteins are direct inhibitors of anti-apoptotic family members including BCL2, BCLXL, BCLw and MCL [reviewed in (55)].

Currently, BH3-mimetics with the most clinical data include GDC-0199 (formerly ABT-199) and its predecessors navitoclax (ABT-263) and ABT-737. ABT-737 was the parent compound, developed based on structure-activity studies evaluating binding pockets of BH3 mimetics (56). However, the intravenous formulation and very short half-life were practical considerations limiting further development. The oral analog ABT-263 (navitoclax) has been tested in a number of smaller phase I and II trials and showed promising activity. Specifically, approximately 20-30% of patients with FL and CLL responded with mainly partial responses but many of which were highly durable (57,58). Unfortunately, navitoclax was associated with a reversible but profound mechanism-related thrombocytopenia attributed to BCLXL inhibition and precluding optimal dose escalation.

Currently, the agent with the most encouraging data and ongoing trials is ABT-199. Like ABT-263, ABT-199 is orally available but has higher specificity for BCL2 and has 500-fold less specificity for BCLXL, thus effectively eliminating mechanism-related thrombocytopenia (59). A single agent phase I trial in a heterogeneous group of relapsed/refractory lymphomas showed significant activity in MCL (59). A concurrent trial in CLL showed responses in over 80% of patients, including patients with adverse risk features such as 17p deletions and bulky disease (60). Importantly, dose-limiting thrombocytopenia was not observed. However, perhaps reflecting the high potency of the drug, life-threatening tumor lysis syndrome (TLS) occurred in a small number of patients and trials currently require prophylaxis and vigilance for TLS. Nevertheless, this may be an important agent in future management of lymphoid malignancies and a number of single agent and combination studies are ongoing.

Epigenetic modulation

The transcription of genes is a highly regulated process that is largely controlled by modifications to chromatin structures. Normally, DNA is tightly wound and protected by histone proteins. Deacetylation of histone proteins, mediated by histone deacetylases (HDAC) keeps genes from being transcribed, whereas acetylation mediated by histone acetyl transferases (HAT) opens the chromatin structure to facilitate transcription. HDAC inhibitors (HDACi) keep chromatin in the open formation, allowing polymerases and DNA transcription machinery to transcribe genes that preferentially are involved in differentiation and growth inhibition [reviewed in (61)]. There are several classes of agents that may modify chromatin structure, including HDACi, hypomethylating agents and histone methyltransferases. In lymphoma, only the HDACi have substantial clinical data thus far.

There are three HDACi approved in North America for use in lymphomas: vorinostat, romidepsin, and belinostat. Vorinostat, the only approved oral HDACi, is active in cutaneous T-cell lymphomas (CTCL). The main benefit of vorinostat was not only the 30% response rate, but the relief of pruritus (62,63). Romidepsin is approved for use in both CTCL and PTCL, based on responses in approximately one-third of patients despite very heavily pretreated disease (64-67); many of the responses were extremely durable although there are no known predictive factors for response. Most recently, belinostat was approved as a single agent for relapsed and refractory PTCL, again with a response rate of approximately 30% in a single arm trial (68).

Overall, HDACi appear most active in T-cell malignancies and combination trials with chemotherapy are underway. Given the innate drug resistance of most T-cell lymphomas, an appealing strategy is to add an HDACi to front-line CHOP chemotherapy. There are currently two ongoing trials of CHOP plus either romidepsin or belinostat.

Summary

The number of new agents either approved or in mature phases of development is a direct reflection of an improved understanding of lymphomagenesis. This review highlights some categories of agents, with a focus on available clinical data, but is far from exhaustive. One of the main challenges going forward will be to find the optimal combinations of agents for clinical use, particularly since no single agent

is curative for any lymphoma. In addition, while oral medications are attractive for a variety of reasons, few of the trials with oral agents have evaluated the optimal duration of treatment. This is particularly relevant for BCR inhibitors. The duration of treatment will impact cost and feasibility of treatment, but may also affect toxicity rates and compliance. Nevertheless, the number of agents available to manage lymphomas is impressive, and the next generation of trials will hopefully focus on individualized application based on either predictive factors or better biologic stratification.

Acknowledgements

Disclosure: The author has served as a consultant to Celgene, Pharmacyclics, Gilead, Janssen, TG Therapeutics.

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Cite this article as: Smith SM. New drugs for the treatment of non-Hodgkin lymphomas. *Chin Clin Oncol* 2015;4(1):14. doi: 10.3978/j.issn.2304-3865.2015.03.01