Current Treatment Options in Oncology
DOI 10.1007/s11864-014-0274-8

Lymphoma (A Engert, Section Editor)

Ibrutinib in B-cell Lymphomas

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Keywords Diffuse large B cell lymphoma · Follicular lymphoma · Mantle cell lymphoma · B-cell receptor signaling · Bruton's tyrosine kinase · Ibrutinib

Opinion statement

The standard frontline therapy for diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle cell lymphoma (MCL) includes the use of chemoimmunotherapy and/or radiation therapy. When patients with these diseases relapse or are refractory to therapy, their diseases are considered incurable outside of the setting of an autologous or allogeneic stem cell transplant, which many patients are not candidates for due to age or comorbidities. The oral Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, targets the B-cell receptor (BCR) signaling pathway that is critical in the survival of these malignancies. It has shown promising activity in certain subtypes of DLBCL, in relapsed or refractory FL, and in relapsed or refractory MCL for which it has recently received FDA approval and should be considered for use in patients in first relapse. Ibrutinib is an oral therapy taken daily that has been well tolerated by patients. Given the high response rates, tolerability, and acceptable toxicities of ibrutinib therapy, it is now being evaluated in combination therapy both in relapsed B-cell malignancies and frontline studies in DLBCL and MCL. Several other promising agents targeting different kinases in the BCR signaling pathway also are currently under investigation.

Introduction

Non-Hodgkin lymphomas (NHL) are a heterogenous group of lymphoproliferative disorders consisting of B-, T-, and NK-cell lymphomas. B-cell lymphomas represent the most common diagnosis with an approximate annual incidence in the United States of 55,000 to 60,000 cases [1]. The frontline therapy for the majority of B-cell lymphomas involves combination chemoimmunotherapy, with a role for radiation therapy in certain instances. When these diseases relapse, they are incurable with standard therapies outside of potential autologous (ASCT) or allogeneic stem cell transplantation.

Bruton's tyrosine kinase (BTK) is an integral kinase in the B-cell receptor (BCR) signaling pathway, critical for B-cell development, differentiation, and signaling as well as for B-cell proliferation and survival [2]. Sig-

Published online: 01 February 2014

naling through the BCR is critical to the viability of certain B-cell malignancies, including diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma. Furthermore, interruption of BCR signaling has been shown to have antitumor activity in these diseases. Targeting of different signaling kinase molecules in this pathway via the use of kinase inhibitors, most successfully the oral irreversible Btk inhibitor, Ibrutinib, recently have demonstrated significant clinical activity in patients with these B-cell NHL subtypes.

Diffuse Large B-Cell Lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy making up approximately 30 % of NHL cases [3]. DLBCL can be classified into subtypes of lymphoma using gene expression profiling (GEP): germinal center B-cell (GCB), activated B-cell (ABC), primary mediastinal B-cell lymphoma (PMBL), and those not able to be classified into one of these three subtypes [4]. Immunohistochemistry (IHC) staining has been used as a surrogate to GEP to differentiate GCB and ABC subtypes. Although it is not standard practice to alter therapy based on cell-of-origin, GCB tumors are associated with an improved outcome using standard therapy.

Frontline treatment options for DLBCL are based on stage. Patients with localized (Stage I-II) disease can be successfully treated with combined modality therapy using chemoimmunotherapy with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) for three cycles followed by involved field radiation (IFRT) [5] or with chemoimmunotherapy alone using six cycles of R-CHOP [6]. The standard treatment for patients with advanced stage disease is six cycles of R-CHOP [7]; however, R-EPOCH (rituximab, etoposide, cyclophosphamide, doxorubicin, vincristine, prednisone) also is acceptable in selected situations [8].

Follicular Lymphoma

Follicular lymphoma (FL) is the most common type of indolent lymphoma making up approximately 20 % of NHL cases [3]. FL is characterized by the translocation, t(14;18), leading to deregulated expression of BCL2. The standard frontline therapy for FL has historically been based on stage. The standard therapy for early-stage (Stage I-II) FL is considered to be IFRT with a median overall survival (OS) of 14 years and 15-year progression-free survival (PFS) of 40 % [9]. Studies have suggested that chemoimmunotherapy or a combined modality approach with chemotherapy and radiation prolong PFS compared with radiation alone, observation, or single-agent rituximab; however, no differences in overall survival have been observed [10, 11]. In patients with advanced stage disease (Stage IIB, Stage III-IV) with low tumor burden or asymptomatic disease, there is no survival benefit with early therapy compared with observation until clinical indication for treatment [12]. Dependent upon indication for treatment, treatment options include single-agent rituximab [13] or combination chemoimmunotherapy [14]. Rituximab in combination with Bendamustine (BR), CVP (cyclophosphamide, vincristine and prednisone), or CHOP are all acceptable therapies [15-17]. Although treatment with BR and R-CHOP have similar overall response rates, treatment with BR does give an improvement in complete response and PFS and also is associated with less toxicity than R-CHOP [17]. BR can be considered the standard for many patients. The addition of rituximab maintenance after combination chemotherapy also plays a role in follicular lymphoma as it has been shown to prolong PFS [18].

Mantle Cell Lymphoma

Mantle cell lymphoma (MCL) is an intermediate B-cell lymphoma making up approximately 6 % of NHL cases [3]. MCL is characterized by the translocation t(11;14), with expression of Cyclin D1. There is no standard frontline therapy for MCL. Several treatment regimens have activity in newly diagnosed disease, but none of these regimens are currently considered to be curative. The treatment strategy for MCL has historically been based on age and comorbidities, with the younger (≤65 years), fit patients being treated with more aggressive frontline therapy, including autologous stem cell transplant, whereas older patients or those unable to tolerate more aggressive therapy are treated on clinical trial or with less intensive single-agent or combination chemotherapy.

Frontline therapy in the younger population includes intensive chemoimmunotherapy and ASCT. Compared with treatment with R-CHOP, which has a PFS of approximately 18 months [19], regimens have median PFS of 39 months to 6 years in this younger group of patients, such as R-CHOP followed by ASCT; R-Hyper-CVAD (rituximab, cyclophosphamide, doxorubicin, vincristine, dexamethasone) alternating with R-methotrexate and cytarabine; augmented R-CHOP alternating with R-high dose cytarabine followed by ASCT (Nordic MCL2); augmented R-CHOP plus methotrexate with etoposide/cytarabine/rituximab mobilization and ASCT (CALGB 59909 Damon Regimen);

and R-CHOP alternating with R-DHAP (dexamethasone, cytarabine and cisplatin) followed by ASCT [20-26]. While these regimens have improved upon PFS, they are associated with greater risk of toxicity and treatment-related mortality and therefore are not considered as options in many patients. For older patients or patients not able to tolerate ASCT, frontline treatment includes BR or R-CHOP with maintenance rituximab until progression [17, 27].

Treatment

- When patients with DLBCL, FL, or MCL relapse, several treatment options are available, including aggressive combination salvage therapy, ASCT, allogeneic transplant, clinical trial, or novel agents. For patients not eligible for a curative approach with ASCT or allogeneic transplant due to disease features, comorbidities, patient age, or lack of suitable donor, therapy should focus on prolonging progression-free survival and overall survival while minimizing toxicity. Patients should be treated on a clinical trial if possible, with standard therapeutic options, including further chemotherapy, immunomodulatory agents, and targeted therapy. This review will focus on these treatment options.

Pharmacologic Treatment

Standard Chemotherapy

- Chemoimmunotherapy is standard for the frontline treatment of DLBCL, FL, and MCL as listed above.
- In patients with DLBCL with relapsed or refractory disease sensitive to chemotherapy at the time of relapse, high-dose chemotherapy followed by ASCT is the treatment of choice if the patient is a candidate for such therapy. This has been shown to prolong 5-year event free survival (46 % vs. 12 %) and 5-year overall survival (53 % vs. 32 %) compared with chemotherapy alone [28].
- Several different regimens can be used before ASCT, none of which has been shown to be superior. The CORAL study, an international randomized intergroup study, compared R-DHAP (dexamethasone, cisplatin, cytarabine) with R-ICE (ifosfamide, carboplatin, etoposide) and found no significant difference in treatment outcomes. Overall response rate was 64 % after both therapies with 4-year, event-free survival of 37 % with R-DHAP compared with 26 % with R-ICE and 4-year overall survival of 51 % compared with 43 % respectively [29]. Other reasonable options include rituximab in combination with GDP (gemcitabine, dexamethasone, cisplatin) and ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin) [30, 31].
- In relapsed or refractory FL, chemotherapy options include any of the frontline therapies discussed above (BR, R-CHOP, R-CVP) that was not utilized in initial treatment or any of the options listed above for relapsed or refractory DLBCL.
- In relapsed or refractory MCL, for patients that have not received prior bendamustine, BR is an effective therapy with overall response rates of 75-92 % with complete response rates of 42-50 % [32, 33]. Options listed above for relapsed or refractory DLBCL also can be utilized.

Lenalidomide

- Lenalidomide (Revlimid; Celgene, Summit, NJ) is an oral immunomodulatory agent with activity in several hematologic malignancies that has FDA approval for the treatment of patients with relapsed mantle cell lymphoma but remains off label for DLCL and FL.
- Lenalidomide has been shown to have activity in DLBCL, FL, and MCL.
- In a phase II study of relapsed or refractory aggressive NHL, 49 patients were treated with 25 mg of oral lenalidomide days 1-21 of 28 days. The objective response rate was 35 % with 12 % complete response. Median progression-free survival was 4.0 months [34].
- In a phase II study of relapsed or refractory indolent NHL, 42 patients were treated with 25 mg of oral lenalidomide days 1-21 of 28 days. The objective response rate was 23 % with 7 % complete response [35].
- The addition of rituximab to lenalidomide was shown to improve upon outcomes in FL. In a randomized phase II study, patients with relapsed or refractory FL were treated with lenalidomide 20 mg oral days 1-21 of 28 days alone or in combination with rituximab weekly for 4 weeks. Forty-five patients were treated with single-agent lenalidomide and four-four patients with combination therapy. Overall response rate was 49 % with 13 % complete response with single agent lenalidomide and 75 % overall response with 32 % complete response in combination therapy. Event-free survival was 1.2 years in the single-agent lenalidomide group and 2.0 years in the patients with combination therapy [36].
- Two phase II studies have been done in relapsed or refractory MCL treating a combined 72 patients with overall response rates 42-53 %, complete responses of 17-20 % and median progression free survival of 6 months [37•, 38], leading to its FDA approval in this disease. A study using combination therapy with rituximab and lenalidomide 20 mg days 1-21 of 28 showed an overall response rate of 57 % with 36 % complete response and median progression-free survival of 11 months [39].
- Lenalidomide received FDA approval for relapsed or refractory MCL in June 2013.
- Lenalidomide is currently under evaluation in the frontline setting in combination with chemotherapy in DLBCL and in combination with rituximab in FL and MCL.
- The combination of lenalidomide and rituximab in previously untreated follicular lymphoma was evaluated in a multicenter, phase II study. Patients with bulky stage II, III-IV disease where treated with lenalidomide 20 mg oral days 1-21 of 28 days for 12 cycles in combination with 4 weekly rituximab treatments cycle 1 and day 1 of

cycles 4, 6, 8, and 10. Fifty-one patients were evaluable for response overall response rate 92.6 % and 72.2 % complete response rate. Although longer follow-up is needed for adequate PFS assessment, response rates are promising [40] (NCT 01145495).

- This combination is currently being evaluated in previously untreated mantle cell lymphoma. Patients who were not eligible for intensive therapy with ASCT were treated with induction therapy with lenalidomide 20 mg oral days 1-21 of 28 days and 4 weekly rituximab treatments cycle 1 and day 1 of cycles 4, 6, 8, 10, and 12. Patients were then continued on maintenance therapy with lenalidomide 15 mg oral days 1-21 of 28 days and rituximab every 8 weeks until progression. Interim results reported a total of 31 patients treated with an overall response rate of 77 % and a complete response of 40 % [41] (NCT01472562).
- Toxicity associated with lenalidomide includes hematologic toxicity, rash, tumor flare, and DVT. Aspirin prophylaxis is recommended with therapy.

Bortezomib

- Bortezomib (Velcade; Millennium, Cambridge, MA) is a proteosome inhibitor that is FDA-approved for use in relapsed or refractory MCL based on the PINNACLE study. Treatment dosing is 1.3 mg/m^2 days 1, 4, 8, and 11 every 21 days. Treatment with bortezomib has an overall response rate of 33 %, complete response of 8 % and median time to progression of 6.7 months [42•, 43]. Peripheral neuropathy and lymphopenia are the most common toxicities. Antiviral prophylaxis is recommended with therapy.

Ibrutinib

- Ibrutinib (PCI-32765 (Imbruvica); Pharmacyclics, Sunnyvale, CA) is a selective and irreversible small molecule inhibitor of BTK. In vitro data showed selective toxicity to DLBCL cell lines dependent upon chronic active BCR signaling [44].
- A Phase I study of Ibrutinib in relapsed B-cell malignancies suggested activity in a number of different NHLs. This study enrolled 56 patients with various histologies, including DLBCL, MCL, FL, chronic lymphocytic leukemia (CLL), marginal zone lymphoma (MZL), and Waldenström's macroglobulinemia (WM). This established the dose of 560 mg orally daily as recommended for further study. Ibrutinib was well tolerated with most adverse events being grade 1 or 2. Only two dose-limiting toxicities were reported, one a grade 3 allergic hypersensitivity that occurred in a patient with a history of allergic reactions and one for dose interruption for more than 7 days secondary to grade 2 neutropenia that resolved. The majority of adverse events were grade 1-2, with the most common being diarrhea, nausea/vomiting, anorexia, fatigue, and myalgias. Of the 50 patients evaluable for response, 30

(60 %) had an objective response with 8 (16 %) complete responses (CR). Specifically, responses were seen in 2 of 7 patients with DLBCL, 7 of 9 patients with MCL, 6 of 16 patients with FL, 11 of 16 patients with CLL, 1 of 4 patients with MZL, and 3 of 4 patients with WM. Median progression-free survival was 13.6 months [45•].

- The activity and tolerability seen in this phase I study led to several phase II studies in different B-cell malignancies, including DLBCL, FL, MCL, CLL, and Waldenström's macroglobulinemia.
- A phase II, multicenter study of single agent ibrutinib in relapsed/refractory DLBCL enrolled 70 patients. All patients enrolled in the study had gene expression profiling done before treatment. This was done to determine if ibrutinib would be more efficacious in the activated B cell (ABC)-type DLBCL compared with the germinal center B cell (GCB)-type DLBCL. Selective activity in the ABC subtype was hypothesized given the constitutive activation of B-cell receptor signaling in the ABC type, which is dependent to an extent on activating mutations including CD79B, MYD88, and CARD11. These somatic mutations cause activation of the BCR pathway and the toll-like receptor pathway, which feeds into the BCR pathway to activate the nuclear factor kappa B (NF-κB) pathway. Patients enrolled had a median age of 64 years and a median of 3 prior therapies. The overall response rate in all patients was 23 % with a complete response rate of 9 %. When responses were evaluated by subtype, the overall response rate in the 29 patients with ABC type was 41 %, whereas overall response rate in the GCB type was only 5 %. Progression-free survival was 5.5 months with 60 % of patients remaining on study and one patient who responded being able to proceed with ASCT. The overall survival was 9.7 months in the ABC type compared with 3.4 in the GCB type. Furthermore, ibrutinib had activity in patients with and without CD79b mutations, suggesting an alternative mechanism of BCR pathway dependence and combination CD79b and MYD88 mutations but not those with sole MYD88 or CARD11 mutations, suggesting a BCR-independent role in ABC lymphoma. This indicates that further study of ibrutinib should be aimed at the ABC type of DLBCL, with attention to the different somatic mutations [46••].
- Updated data from the cohort of patients with follicular lymphoma treated in the Phase I study included 16 patients with a median age of 60 years and median number of 3 prior therapies. Of the cohort of 16 patients, 11 patients were treated at doses where full occupancy of BTK was achieved by ibrutinib. The overall response rate in these 11 patients was 55 % with 3 complete responses and 3 partial responses. The median duration of response was 12.3 months and the median PFS 13.4 months. Based on this promising data, there is an ongoing Phase II study of ibrutinib in relapsed/refractory follicular lymphoma in patients who have received at least two prior regimens [47] (NCT01849263).
- Results of a phase II, multicenter study of ibrutinib in relapsed/refractory MCL were published in the *New England Journal of Medicine*

in June 2013. In this study, two cohorts of patients were treated with single-agent ibrutinib: those who had received prior therapy with bortezomib and those who were bortezomib-naïve. A total 111 patients were treated, 63 patients who were bortezomib-naïve and 48 patients who had received prior bortezomib. Patients had a median three prior therapies. A 68 % overall response rate was observed with a complete response of 21 % and estimated median PFS of 13.9 months, with no difference in those with prior bortezomib therapy versus those without. Additionally, the overall response rate and the complete response rated improved over time with continued therapy. The median duration of response was 17.5 months. Ibrutinib was well tolerated with grade 3 or higher hematologic adverse events being infrequent and the most common adverse treatment-related events being diarrhea, fatigue, and nausea [48••].

- Based on the results from the above phase II study in MCL, ibrutinib at a dose of 560 mg orally daily received FDA approval as single-agent therapy in patients with relapsed/refractory MCL with at least one prior therapy in November 2013.
- Ibrutinib is generally well tolerated. Adverse events occurring in more than 20 % of patients in the above studies included diarrhea, nausea, vomiting, fatigue, peripheral edema, upper respiratory infection, and anorexia. Bleeding events from bruising to rare cases of major hemorrhage were reported with ibrutinib and therefore coadministration of antiplatelet and anticoagulant therapy, particularly warfarin, should be avoided. Consideration should be given to holding therapy 3-7 days before and after any procedure.
- Ibrutininb is metabolized by cytochrome P450 enzyme 3A and therefore coadministration with CYP3A strong inhibitors should be avoided long-term, with dose interruption with short-term use and dose reduction of ibrutinib should be considered with long-term use of moderate inhibitors. Coadministration of strong inducers of CYP3A also should be avoided.
- The cost of ibrutinib is approximately $91.00 per pill (140 mg capsules) with four capsules needed daily for a cost of approximately $11,000 per month and $132,000 a year.

Ibrutinib in Combination Therapy in Relapsed or Refractory Disease

- There are several ongoing studies looking at the combination of ibrutinib with other agents in the relapsed and refractory population of patients.
- There is an ongoing Phase I dose-escalation study of BR and Ibrutinib in relapsed or refractory B-cell malignancies with expansion cohorts in DLBCL, MCL, and FL (NCT01479842). A total of 11 patients were enrolled in the Phase I portion with no dose-limiting toxicities observed thus far with current dosing at 560 mg of ibrutinib with standard BR. The most common toxicity serious adverse events reported were hematologic. The overall response rate was 38 %. Ac-

crual is ongoing with planned expansion in the above cohorts [49].
- There is an ongoing Phase I study of ibrutinib in combination with lenalidomide for all B-cell malignancies (NCT01955499).
- There is an ongoing Phase II study of ibrutinib in combination with Rituximab in MCL (NCT01880567).

Ibrutinib in Frontline Therapy

- There is no evidence for use or inclusion of ibrutinib in frontline therapy for any subtype of lymphoma; however, there is significant interest given the efficacy, tolerability, and ease of administration and several studies are ongoing.
- A multicenter phase IB study of R-CHOP in combination with ibrutinib in CD20+ NHL (DLBCL, FL, MCL) is being conducting to determine the maximum tolerated dose of combination therapy with an expansion cohort in DLBCL. A total of seventeen patients were enrolled in the dose finding portion and 16 patients in the expansion. Dose-limiting toxicities included syncope, periorbital cellulitis, and gastritis. The maximum tolerated dose of the combination therapy was 560 mg of ibrutinib with standard R-CHOP. The most common serious adverse events were hematologic. The overall response rate in all evaluable patients was 100 % with complete response 73 % in the initial patients and 60 % in the DLBCL expansion [50] (NCT01569750).
- There is an ongoing randomized, placebo-controlled, multicenter, phase III trial in untreated DLBCL of the non-GCB subtype patients comparing R-CHOP to R-CHOP + Ibrutinib (NCT0185750).
- There is an ongoing randomized, placebo-controlled, multicenter, phase III trial in untreated MCL patients comparing BR to BR and ibrutinib (NCT01776840) in patients who are age 65 years or older.
- There is an ongoing, phase I, multicenter trial in untreated Stage II-IV follicular lymphoma stage evaluating the combination of rituximab, lenalidomide, and ibrutinib (NCT01829568).

Emerging Therapies

- Several other therapies targeting inhibition of the B-cell receptor signaling pathway are in development.
- Idelalisib (GS1101, Gilead) is a selective inhibitor of PI3 Kinase delta, which is critical for survival of B cells and overactive in many B-cell malignancies. Idelalisib was evaluated in NHL patients who were refractory to both rituximab and alkylating agents ("double-refractory"). Idelalisib was given 150 mg of oral twice daily. A total of 125 patients with a median age of 64 years and a median number of four prior therapies were enrolled. The most common toxicities were di-

arrhea, fatigue, nausea, cough, fever, dyspnea, rash, and pneumonia. The overall response rate was 57 % with complete response of 6 %. 90 % of patients experienced some degree of decrease in tumor burden. Median duration of response was 12.5 months and median progression free survival was 11 months. Median overall survival was 20.4 months. Overall, the drug was well tolerated with acceptable toxicities and efficacious in this population of patients [51].

- ABT-199/GDC-0199 (RG7601, Roche) is a bcl-2 inhibitor. Bcl-2 proteins are expressed at high levels in NHL and impact malignant cell growth. ABT-199 works by blocking the function of these proteins and promoting cell death. A phase I study of 32 patients with relapsed or refractory NHL showed an overall response rate of 53 % with 9 % complete response. In the six patients treated with MCL, there was a 100 % overall response rate. Most common toxicities were nausea, diarrhea, vomiting, fatigue, fever, and cough [52].
- IPI-145 (Infinity) is a PI3 Kinase delta and gamma inhibitor. A Phase I dose-escalation study of IPI-145 enrolled 31 patients with relapsed or refractory B-cell malignancies. The maximum tolerated dose was 75 mg oral twice daily with dose-limiting toxicities of rash and transaminitis. The most common serious adverse events were neutropenia and transaminitis. The overall response rate was 52 % [53].
- Other targeted therapies currently being investigated include SYK (spleen tyrosine kinase) inhibitors, novel proteasome inhibitors (carfilzomib; Onyx, San Francisco, CA), antibody-drug conjugates including the anti-CD22 DCDT2980S (Genentech, San Francisco, CA) and the anti-CD79B DCDS4501A (Genentech, San Francisco, CA), aurora kinase inhibitors (alisertib; Millenium, Cambridge, MA) [54], and more specific BTK inhibitors.

Conflict of Interest

Kami Maddocks and Kristie A. Blum have both received research funding from Pharmacyclics.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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