Targeted therapies in B-cell non-Hodgkin lymphomas

The incidence of non-Hodgkin lymphomas has risen in recent years. Although several chemotherapy regimens are efficacious in non-Hodgkin lymphoma, the addition of targeted therapies has become an indispensable part of their treatment. Monoclonal antibodies directed against lymphocytes in different stages of maturation have changed the treatment paradigm for lymphoma. Since these antibodies bind with high affinity to cell surface antigens, they target malignant cells and spare normal tissue, thereby causing less nonspecific toxicity. Rituximab, a monoclonal antibody directed against CD20, was the first antibody to be US FDA-approved for the treatment of lymphoma. Several clinical trials are ongoing that will help to establish the role of targeted agents in the treatment of non-Hodgkin lymphoma. This review provides a summary of targeted agents already approved or in clinical trials for the treatment of non-Hodgkin lymphoma.

KEYWORDS: mAbs ■ monoclonal antibodies ■ non-Hodgkin lymphoma ■ radioimmunoconjugates ■ rituximab ■ targeted therapies

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Non-Hodgkin lymphomas (NHLs) are increasing in incidence and will be diagnosed in more than 55,000 individuals this year alone [1,2]. The 13 most frequent clinical classes recognized in the lymphoma classification include diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), small lymphocytic lymphoma (SLL) mantle cell lymphoma (MCL), peripheral T-cell lymphoma (PTCL), marginal B-cell lymphoma of mucosa associated lymphoid tissue (MALT), primary mediastinal large B-cell lymphoma, anaplastic large T/null cell lymphoma, lymphoblastic lymphoma, Burkitt-like lymphoma, marginal zone B-cell lymphoma of the nodal type, lymphoplasmacytic lymphoma and Burkitt lymphoma [3].

The ultimate goal of any tumor therapy involves the destruction of tumor cells by targeting tumor-specific surface or intracellular properties and thereby sparing normal tissue [4]. In NHL, monoclonal antibodies binding to antigens specific to lymphocytes in different stages of maturation have recently changed the treatment paradigms for this disease. Some of the antigens being targeted include CD20, CD22, CD19, CD37 and CD80 on B-cell surface; and CD52, CD4, CD3 and CD8 on T cells [4].

Antibody-targeted therapy in aggressive lymphomas

Aggressive lymphomas are potentially curable with chemotherapy. These lymphomas include: DLBCL and its variants, Burkitt lymphoma, PTCL, immunodeficiency-associated lymphoproliferative disorder, precursor B lymphoblastic leukemia/lymphoma, and precursor T lymphoblastic leukemia/lymphoma [5].

■ Diffuse large B-cell lymphoma

Anti-CD20 antibody: rituximab

Diffuse large B-cell lymphoma is the most frequently diagnosed NHL [3]. Cyclophosphamide, adriamycin, vincristine and prednisone administered every 21 days (CHOP-21) used to be the 'gold standard' of upfront therapy for DLBCL and resulted in an overall survival of 30–40% at 5 years [6,7]. The addition of rituximab, a therapeutic antibody directed against a pan B-cell antigen CD20, altered the treatment paradigm for DLBCL. Rituximab is a chimeric anti-CD20 human IgG1 monoclonal antibody US FDA-approved for treatment of DLBCL. Phase II studies of rituximab with CHOP (R-CHOP) demonstrated safety in patients with DLBCL [8,9]. This led to several prospective, randomized Phase III studies. In a landmark study of R-CHOP versus CHOP in previously untreated elderly patients with DLBCL, the French study group Groupe d'Etude des Lymphomes de l'Adulte (GELA) demonstrated a 7-year progression-free survival of 52% for R-CHOP-21 versus 29% for CHOP-21 ($p < 0.001$), and an overall survival of 53% for R-CHOP-21 versus 36% for CHOP-21

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(p = 0.004). Benefit was observed in patients with low risk, as well as high-risk, International Prognostic Index [10].

The Intergroup/Eastern Cooperative Oncology Group trial (ECOG 4494) [11,12] also demonstrated that the addition of rituximab to CHOP-21 or CHOP-14 significantly improves the outcome of elderly patients with aggressive B-cell lymphomas. In the analysis of this study, R-CHOP significantly decreased the risk of treatment failure compared with CHOP alone (hazard ratio: 0.64; 95% CI: 0.47–0.85; p = 0.003) with an estimated failure-free survival of 52% for R-CHOP and 39% for CHOP. The second random assignment in responders to maintenance rituximab failed to demonstrate a benefit after R-CHOP at the initial report and at follow up in 5.5 years.

A Canadian population study confirmed the overall survival advantage of R-CHOP versus CHOP [13]. This was a retrospective study of patients in the pre-rituximab era treated with CHOP-like chemotherapy versus the post-rituximab era where patients were treated with rituximab 24–72 h after each CHOP infusion.

The recently published RICOVER-60 study by the German High Grade Lymphoma Study Group (DSHNHL) treated elderly patients with aggressive lymphomas with 6–8 cycles of CHOP-14 or R-CHOP-14 (time interval between courses of 14 days) [14]. The best results were seen with R-CHOP-14, with event-free survival and overall survival of 67 and 78%, respectively.

The Mabthera International Trial (MINT) study was an international trial in young newly diagnosed good-risk patients with DLBCL [15]. This study demonstrated that the addition of rituximab to six courses of CHOP or CHOP-like chemotherapy improved 3-year event-free survival to 79% (95% CI: 75–83) versus 59%, (95% CI: 54–64) and increased 3-year survival to 93% (95% CI: 90–95) versus 84% (95% CI: 80–88).

Rituximab in salvage therapy

The standard of care for DLBCL with primary refractory or recurrent disease typically involves salvage therapy followed by high-dose therapy with stem cell transplantation. In Phase II trials, the addition of rituximab to salvage chemotherapy regimens may improve the overall response rate (ORR) with ifosfamide, carboplatin and etoposide (ICE) and dexamethasone, high-dose cytarabine and cisplatin (DHAP) [16,17]. Currently, a randomized Phase III study is comparing R-DHAP with R-ICE followed by carmustine–cytarabine, etoposide, melphalan (BEAM) high-dose therapy and autologous stem cell transplant [18].

Anti-CD20-based radioimmunoconjugates

One approach to improve the cytotoxic potential of monoclonal antibodies is to attach them to radionuclides to form a radioimmunoconjugate. Experience with radioimmunotherapy in NHL is largely limited to the relapsed, refractory settings. Currently, two drugs are registered in the USA: ^{90}Y-ibritumomab tiuxetan (Zevalin®, Genentech [CA, USA] and BiogenIDEC [MA, USA]) and ^{131}I-tositumomab (Bexxar®; GlaxoSmithKline [Middlesex, UK]).

Ibritumomab, a murine anti-CD20 antibody, is labeled to Yttrium-90 to form ^{90}Y-ibritumomab tiuxetan. Unlabeled rituximab is infused prior to the radiolabeled product to improve biodistribution. A nonrandomized multicenter Phase II study was conducted to study the safety and efficacy of a single dose of this drug in patients with relapsed/refractory DLBCL who were not candidates for stem cell transplant. The ORR to ^{90}Y-ibritumomab tiuxetan was 19% in patients who were previously treated with rituximab [19]. The ORR was 52% in patients who failed induction therapy and 53% in patients who relapsed after complete remission (CR). The median progression-free survival/overall survival was 5.9 months/21.4 months in those for whom induction therapy failed, 3.5 months/22.4 months in patients who relapsed after CR and 1.6 months/4.6 months in patients who were treated with chemotherapy and rituximab, respectively. Two patients died of cerebral hemorrhage associated with grade 4 thrombocytopenia; 43% patients experienced grade 3 or 4 hematological toxicities.

In a Phase I/II trial of ^{90} Y-ibritumomab tiuxetan the ORR was 43% in patients with intermediate-grade histology [20]. In long-term follow-up, 58% of patients with DLBCL had a response, with a median duration of response of 49.8 months [21]. In a Phase II trial of R-CHOP followed by Y-ibritumomab tiuxetan in high-risk patients (International Prognostic Index 2 and 3) the intent to treat overall survival was 63% and event-free survival was 59%. All patients who received ibritumomab tiuxetan remained relapse-free at a median of 21 months [22].

Tositumomab is a murine monoclonal antibody that binds to CD20 and is radiolabeled to Iodine-131. This has been evaluated in five studies in patients who are not candidates for stem cell transplantation and have undergone

a median of four prior therapies [23]. A CR rate of 25% and an ORR of 39% has been observed at a median follow up of 19.4 months. The median duration of response was 20 months and median time to progression was 4.2 months in all patients.

A Phase I/II trial of tositumomab, in place of total-body irradiation, in combination with high-dose etoposide and cyclophosphamide followed by autologous stem cell transplant demonstrated promising therapeutic outcomes [24].

Anti-CD22 antibody epratuzumab

One of the antigens expressed on B cells is a siaglycoprotein, CD22, expressed by pre-B cells and mature B cells and expressed in 85% of DLBCL. Epratuzumab is a monoclonal IgG1 antibody targeting CD22. This drug works by signal activation and induction of antibody-dependent cell cytotoxicity [25].

This drug has been studied either alone or in combination with R-CHOP in Phase I and II trials in both indolent and aggressive lymphomas. In indolent lymphomas eptratuzumab was associated with an ORR of 18 and 58%, a CR rate of 6 to 28% and time to progression of more than 2 years [26–28]. In aggressive lymphomas it was associated with an ORR of 10% and time to progression of more than 6 months [26].

Anti-CD40 antibody SGN-40

SGN-40 is a humanized monoclonal antibody against CD-40, a member of the TNF receptor family expressed in some solid tumors, most B-cell malignancies (including NHL, myeloma and chronic lymphocytic lymphoma) and Hodgkin lymphoma. SGN-40 can induce apoptosis and antibody-dependent cellular cytotoxicity [29]. A Phase I trial with SGN-40 in patients with recurrent NHL, including DLBCL, demonstrated this to be a well tolerated drug with a CR rate of 37.5% after completion of one cycle [30]. A number of studies are currently evaluating SGN-40 as a single agent in relapsed DLBCL. A randomized Phase II study is comparing ifosfamide, carboplatin, etoposide and rituximab (R-ICE) with and without SGN-40 for second-line treatment in patients with relapsed/refractory DLBCL [31].

Immunomodulators

Immunomodulators are immunomodulating agents that are structural and functional analogs of thalidomide. They have been found to have activity in several diseases, including multiple myeloma [32–34], myelodysplastic syndrome [35,36] and chronic lymphocytic lymphoma [37,38].

A US-based Phase II study of lenalidomide monotherapy in relapsed or refractory aggressive NHL demonstrated an ORR of 34% for all patients and 24% for DLBCL patients, with a median time-to-progression of approximately 7 months in responders [39]. A larger international trial in the same relapsed aggressive B-cell lymphoma population has reached accrual and preliminary results appear to validate the earlier, smaller Phase II study [40]. Lenalidomide was also seen to have significant activity in MCL, grade 3 FL and transformed lymphoma [39,40]. The drug is well tolerated with myelosuppression being dose-limiting. Cytopenia poses the most difficult problem for combining lenalidomide with other chemotherapy agents [31]. More than ten different studies investigating lenalidomide in different histologies of lymphomas, as well as in combination with different chemotherapy agents, are ongoing.

mTOR inhibitors

Mammalian target of rapamycin (mTOR) inhibitors have been used in lymphomas, including DLBCL. Rapamycin is known to affect the pathway that is important for lymphoma cell survival and proliferation [41–44]. Temsirolimus is an mTOR inhibitor that demonstrated activity in a Phase II study of patients with relapsed and refractory NHL, including DLBCL. There was an ORR of 40% across all histologies of NHL [41].

Everolimus, another mTOR inhibitor, also has been shown to have some activity in lymphomas, including DLBCL [44–46]. In a Phase II trial of patients with relapsed or refractory aggressive lymphomas objective responses were seen in six out of 12 patients [46].

Fostamatinib disodium (Syk inhibitor)

Certain normal and malignant B cells rely upon B-cell receptor (BCR)-mediated survival signals. BCR signaling causes recruitment and activation of spleen tyrosine kinase (SYK). SYK thereby initiates downstream events and amplifies the original BCR signal. A subset of DLBCL exhibits overexpression of BCR pathway components, including SYK. Fostamatinib disodium (FosD) is an orally available inhibitor of SYK under development for rheumatoid arthritis, which has also demonstrated significant *in vitro* activity against BCR-dependent NHL. A Phase I trial of FosD in patients with relapsed and refractory DLBCL was undertaken. Two different doses of the drug were assessed and the dose of 200 mg twice a day was used for Phase II studies. A total

of 68 patients were enrolled with relapsed/refractory NHL in three separate disease cohorts: DLBCL (n = 23); FL (n = 21) and other B-cell NHL (n = 24) including SLL/chronic lymphocytic lymphoma (n = 11), MCL (n = 9) marginal zone/MALT (n = 3) and lymphoplasmacytic NHL (n = 1). The median age of patients in the Phase II trial was 61 (range 41–87) years; patients received a median of five prior therapies, including autologous stem cell transplantation (16; 12 with DLBCL) and radioimmunotherapy [8]. FosD was overall very well tolerated. Best responses by disease histology were as follows: DLBCL 21% (four partial remission [PR]; one CR); SLL/chronic lymphocytic lymphoma 54% (six PR); FL 10% (two PR); MCL 11% (one PR). Stable disease was observed in an additional 23 patients, including 12 with FL, four with DLBCL, four with MCL, two with chronic lymphocytic lymphoma/SLL and one with MALT [47]. This study is currently ongoing.

Aggressive T-cell lymphomas

Approximately 15% of the NHLs are T cell in origin. The subgroup of PTCL, not otherwise specified (PTCL and myelodysplastic syndromes), represents the largest group of T-cell lymphomas in the REAL/WHO classification [3,48]. PTCLs have the worst overall and failure-free survival. Some of the antibodies being targeted in T-cell lymphomas include CD2, CD4, CD30 and CD52.

Alemtuzumab

Alemtuzumab is a humanized anti-CD52 IgG1 monoclonal antibody (Campath [Bayer HealthCare Pharmaceuticals Inc.]) and has been used therapeutically in the treatment of B-chronic lymphocytic lymphoma, but is being increasingly used in PTCL. When used as a single agent the response rate was approximately 36% in refractory PTCL [49]. It was associated with severe toxicities including cytomegalovirus activation, pulmonary aspergillosis, pancytopenia and Epstein–Barr related hemophagocytosis. Currently, a prospectively randomized Phase III trial is assessing the role of alemtuzumab in combination with CHOP chemotherapy as first-line therapy of PTCL [50].

Denileukin diftitox

Denileukin diftitox (Ontak®) targets the intermediate and high-affinity IL-2 receptors. It is fused to diphtheria toxin, which when internalized into a cell inhibits protein synthesis. This was the first drug approved by the FDA for cutaneous T-cell lymphoma. In a Phase III clinical trial in pretreated patients with cutaneous T-cell lymphomas an ORR of 30% was seen, with improvement in quality of life in both responders and nonresponders [51,52]. In patients with aggressive PTCLs a 48% response rate was demonstrated at a dose of 18 µg/kg/day. The progression-free survival was 6 months, with several patients experiencing 2-year progression-free survival [53]. Denileukin diftitox has also shown activity in fludarabine refractory B-chronic lymphocytic lymphoma [54] and in steroid-refractory acute graft versus host disease after allogeneic hematopoietic stem cell transplantation [55].

Siplizumab

Siplizumab is a monoclonal antibody against CD2, a pan-T-cell antigen that is expressed on many T-cell lymphomas including PTCL and extranodal T/natural killer cell lymphoma, nasal type. This humanized monoclonal antibody has been studied in adult T-cell leukemia and is now being studied in Phase I trials in other lymphoproliferative disorders [101].

Histone deacetylase inhibitors

Histone deacetylase (HDAC) inhibitors function through several diverse mechanisms, including promotion of cell cycle arrest, apoptosis and inhibiting angiogenesis. Several HDAC inhibitors are under investigation, including vorinostat, which was recently approved for the treatment of cutaneous T-cell lymphoma (i.e., in patients with progressive, persistent or recurrent disease after two systemic therapies). In a Phase II trial of oral vorinostat in 33 patients with refractory cutaneous T-cell lymphoma, eight patients achieved a PR and 14 patients had relief from pruritus [56]. In a single open-labeled trial conducted at 18 centers in the USA and Canada 74 patients were enrolled with stage 1B or higher cutaneous T-cell lymphoma in whom two systemic therapies had failed (one of which must had contained bexarotene). At a dose of 400 mg daily (which could be reduced to 300 mg for toxicity), 30% of the patients attained responses; the estimated median duration of response was 168 days and median time to tumor progression was 202 days [57].

Another HDAC inhibitor, FK-228 (depsipeptide), has also shown activity in PTCL with responses lasting 8–14 months, with seven out of 14 patients obtaining objective responses. Based on these results multicenter trials of FK-228 have been initiated in patients with PTCL or cutaneous T-cell lymphoma [58].

Antibody therapies in indolent lymphomas

Follicular lymphomas

The combined group of FLs make up the second most common type of NHL. These lymphomas are classified as FL grade 1, 2, 3a or 3b in the WHO classification schema.

Anti-CD20 antibody: rituximab

The addition of rituximab to the previously known therapeutic options for FL has altered the clinical course of patients with FL. In contrast to patients with aggressive lymphomas, the situation with FLs (grades 1, 2, 3a) is different because rituximab can be effectively used as a single agent or together with chemotherapy. Furthermore, maintenance with rituximab after any of these regimens can improve outcomes.

Several studies have evaluated the effect of rituximab as a frontline agent [59,60]. The ORR has been in the order of 75% with almost half of these patients achieving a CR. However, most patients progressed between 1–2 years after initial therapy and required retreatment. At this time it is not clear whether prolonged treatment with rituximab [61] or retreatment at the time of relapse [62] will ultimately become the standard-of-care.

At least four randomized studies have studied the effect of addition of rituximab to different chemotherapy regimens. When added to cyclophosphamide, vincristine and prednisone (CVP), R-CVP was shown to have a better time to progression and duration of response in patients with untreated stage III/IV CD20-positive FL. Median time to progression or death was 34 months in the R-CVP arm compared with 15 months in the CVP arm ($p < 0.0001$). Patients receiving R-CVP had a significant improvement in overall survival compared with CVP (hazard ratio: 0.60; 95% CI: 0.38–0.96) [63]. In a study of patients with untreated advanced-stage FL, R-CHOP was demonstrated to reduce the relative risk of failure by 60% and significantly prolonged the time to treatment failure. In addition, a significantly higher response rate was seen with R-CHOP when compared with CHOP (96 vs 90%; $p = 0.011$) [64].

In another study, previously untreated patients with stage III/IV indolent lymphomas were randomized to eight cycles of mitoxantrone, chlorambucil and prednisolone (MCP) or rituximab plus MCP (R-MCP). Patients achieving a complete or partial remission were treated with interferon (IFN) maintenance until relapse. In the primary analysis, patients with FL had better overall and complete responses in the R-MCP arm than MCP arm (overall response: 92 vs 75%, respectively; $p = 0.0009$; and complete response rate: 50 vs 25%, respectively; $p = 0.004$ [65]).

The FL2000 study was undertaken to evaluate the combination of rituximab with chemotherapy plus IFN as first-line treatment in patients with FL with high tumor burden. Patients were randomly assigned to receive either 12 cycles of cyclophosphamide, adriamycin, etoposide and prednisolone (CHVP) plus IFNα2a or six courses of chemotherapy combined with six infusions of rituximab with IFN. After a median follow up of 5 years, the event-free survival was 37% (95% CI: 29–44%) and 53% (95% CI: 45–60%) in the CHVP + IFN versus R-CHVP + IFN arm ($p = 0.001$), respectively. However, 5-year overall survival estimates were not statistically different in the CHVP + IFN (79%; 95% CI: 72–84%) versus R-CHVP + IFN (84%; 95% CI: 78–84%) arms [66].

Since different chemotherapy regimens have been used and there is no uniformity in the use of consolidation and maintenance therapy it is very difficult to assess the best approach to use to treat patients with FL. It is quite possible that in the future treatment will be individualized using a risk-adapted approach.

Anti-CD20 radioimmunoconjugates

The Phase I/II study of ibritumomab tiuxetan (Y-IT) included a dose-escalation study of the dose of rituximab used pre-infusion in an attempt to optimize the distribution of the radioactive antibody. The minimal optimal dose of rituximab was found to be 250 mg/m^2 [67]. An 82% response rate was noted in patients with relapsed, refractory, rituximab-naive follicular or low-grade lymphoma; median time-to-progression exceeded greater than 1 year. Patients with more than 25% involvement of the bone marrow by disease, radiation to more than 25% of the marrow, prior autologous stem cell transplantations, or a failed attempt at prior autologous stem cell collection were excluded due to a reduced bone marrow reserve.

Following these encouraging results a large randomized study was initiated comparing Y-IT with rituximab in rituximab-naive patients with relapsed or refractory low-grade or transformed lymphoma. Rituximab was given as four weekly infusions. The ORR and CR rate favored Y-IT over rituximab: 80 versus 30% patients; and 56 versus 16%, respectively [68]. The time to progression and duration of response were not statistically different.

A separate study addressed the question of activity in patients whose disease is resistant to rituximab. [69] The study included mostly FL patients with many adverse features and a median of four prior treatments. The overall response to Y-IT was 74%, with a median time to progression for responders of 8.7 months (range: 1.7–25.9 months). For the entire group the time to progression was 6.8 months. In the subset of patients who had a prior brief response to rituximab the response rate was 88% and the median duration of response 11.5 months. This study confirmed the significant therapeutic value of the radioactive component for a radiation-sensitive tumor such as follicular B-cell lymphoma.

In a multivariate analysis of 203 patients the only factor that predicted response was tumor bulk [70]. Patients with nodal masses greater than 5 cm had a 68% response rate and shorter duration of response, whereas smaller tumors had a 90% response rate ($p < 0.001$). Age, prior radiation, extranodal disease and International Prognostic Index score failed to correlate with outcome. Retrospective meta-analysis of the same studies suggests a considerably better outcome for patients treated at the time of first relapse of their lymphoma [71].

A dose-escalation study of I-131 tositumomab established a maximum tolerated dose of 75 cGy total body dose and 475 mg as the optimal tositumomab pre-dose. In patients with low-grade or transformed lymphoma the response rate was 83% compared with 43% in patients with aggressive NHL [72]. A multicenter pivotal trial of 60 patients (60% with low-grade lymphoma) who were rituximab naive and had failed last treatment or had relapsed in the last 6 months was conducted. Bulky disease was present in 65% and bone marrow was involved in 56%. Responses were noted in 65%, and responses were higher for low-grade lymphoma. Improved responses depended on tumor burden, prior radiotherapy and number of prior therapies [73].

A study including previously untreated patients with low-grade follicular NHL indicated a higher activity in early disease [74]. Among 76 patients with follicular small cleaved or mixed cell lymphoma, a response rate of 95% was seen, including 56% CR. After a median follow-up of 43 months the 5-year progression-free survival was 62%.

Based on these studies it can be concluded that ^{131}I-Tositumomab has activity against patients with B-cell lymphoma attributed to targeted irradiation of the tumor plus independent anti-tumor activity from the antibody.

Anti-CD80 antibody: galiximab

CD80 is a transmembrane glycoprotein involved in activation and regulation of T cells [75]. It is transiently expressed on activated B cells and dendritic cells [76]. It also plays a role in the regulation and activation of malignant B cells [77].

A Phase I/II dose-escalation study was carried out to evaluate the safety and efficacy of this antibody. Patients included those with relapsed and refractory FL, stage III/IV (90%). A total of four weekly intravenous infusion of galiximab were administered at doses of 125, 250, 375 and 500 mg/m$_2$. Antibody infusions were safe and well tolerated without any dose-limiting toxicities. The overall objective response rate was 11%. However, nearly half the patients had some decrease in indicator lesions [78]. Of note, the time to response was delayed in the four responders. Maximum reduction in tumor burden was observed at 9 and 12 months in two responders when the serum levels of galiximab were below the level of detection, suggesting a possible T-cell-associated cellular immunity response.

A Phase I/II study of galiximab was carried out in combination with rituximab in patients who had failed or relapsed on primary therapy. A total of 73 patients received treatment, all had received prior treatment and 40% were rituximab-naive. The ORR at the recommended Phase II dose of galiximab (500 mg/m^2) was 66%: 19% CR, 14% unconfirmed CR, and 33% partial response. The median progression-free survival was 12.1 months [79]. These results indicated that galiximab can be safely combined with a standard course of rituximab.

A Phase II trial of extended induction galiximab plus rituximab in untreated FL patients has been completed. It has shown that the extended induction is well tolerated with minimal hematological toxicity. An ORR of 72.1% with CR/unconfirmed CR of 47.6% was observed. Median follow-up is 2.1 years and progression-free survival and disease-free survival have not been reached [80]. One of the conclusions of this study is that rituximab in combination with galiximab is extremely well tolerated and a potentially promising regimen in patients with untreated FL, especially those with low- and intermediate-risk Follicular Lymphoma International Prognostic Index scores.

Histone deacetylase inhibitor: vorinostat

A Phase II study of vorinostat is ongoing in relapsed refractory indolent NHL. Vorinostat

(suberoylanilide hydroxamic acid [SAHA]) is an orally administered hydroxamic acid histone deacetylase inhibitor with activity against class I and II deacetylases, with preclinical and clinical activity against various forms of lymphoma. A total of 37 patients were enrolled in this study (FL, n = 20; MCL, n = 8, marginal zone lymphoma). Treatment with oral vorinostat was well tolerated. By the current Cheson criteria, six patients achieved CR, and four patients achieved PR, for an ORR (CR + PR) of 29% [81].

Conclusion & future perspective

The development of targeted therapies has broadened the treatment options for patients with B-cell lymphomas. There are a significant number of additional exciting targeted agents that are in preclinical and clinical trials (i.e., second- and third-generation anti-CD20 monoclonal antibodies, bortezomib and second-generation proteasome inhibitors, and so on), which have not been discussed in this manuscript due to space limitations. The early results for many of these agents are promising. However, additional clinical studies are needed to evaluate the optimal dose, schedule, and combination of these agents with other active antilymphoma agents. Further research is also needed to evaluate the mechanism of action of many of these targeted agents. This is an exciting era in the treatment of NHLs. The future entails the further development of the therapies mentioned in this article, as well as other novel targets in the treatment of lymphoma, along with a better understanding of their mechanism of actions. This will enable the ultimate goal of 'individualization' of more effective and less toxic treatments based on the targets present on the patient's unique tumor.

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Executive summary

- Monoclonal antibodies binding to antigens specific to lymphocytes at various stages of maturation have changed the treatment paradigm for lymphoma.
- Rituximab was the first anti-CD20 monoclonal antibody to be approved for treatment of lymphoma. In combination with cytotoxic chemotherapy, rituximab has been shown to significantly improve the response rate, progression-free survival and overall survival in patients with both aggressive and indolent lymphoma.
- Anti-CD20 radioimmunoconjugates, ^{90}Y-ibritumomab tiuxetan and ^{131}I-tositumomab, are also US FDA-approved and are clinically active for the treatment of relapsed/refractory indolent lymphoma.
- An anti-CD22 antibody, epratuzumab, and an anti CD-40 antibody, SGN-40, have shown promising activity against B-cell lymphomas in Phase I and Phase II trials.
- Other novel agents being studied in aggressive B-cell lymphomas, include: immunomodulators (like lenalidomide), mTor inhibitors, and Syk inhibitors.
- Anti-CD52 antibody, alemtuzumab, is already approved for the treatment of cutaneous T-cell lymphoma and is undergoing Phase III trials with cyclophosphamide, adriamycin, vincristine and prednisone (CHOP) in the treatment of peripheral T-cell lymphoma.
- Other agents showing promise in aggressive T-cell lymphomas include the histone deacetylase inhibitor family of agents.
- Anti-CD-80 antibody, galiximab, is undergoing Phase I/II/III trials in follicular lymphoma with promising results. A large prospectively randomized galiximab plus rituximab versus placebo plus rituximab trial is currently actively accruing patients with relapsed/refractory follicular lymphoma.
- Targeted agents bind with high affinity to their antigens on malignant cells, thereby largely sparing normal tissue and causing less nonspecific toxicity than cytotoxic chemotherapeutic agents.
- The future entails the ultimate development of individualized targeted therapy for each patient based on a combination of prognostic factors, specific biomarkers and abnormalities in molecular pathways for their unique neoplasm.

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Website

101 Phase I study
www.clinicaltrials.gov/NCT0007536

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