Antibody Therapy in Aggressive Lymphomas

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The aggressive lymphomas are potentially curable. The natural history of certain aggressive lymphomas has been altered by monoclonal antibody therapy. Targeted monoclonal antibody therapy to the CD20 antigen has altered the outcome of patients with diffuse large B-cell lymphoma in patients of all ages. Anti-CD20–based radioimmunoconjugates are being evaluated as radioimmunotherapy approaches in patients who have relapsed and in stem cell transplant settings. Antibody-directed therapy to the B-cell–specific antigen CD22 are ongoing. New approaches include different CD20 antibodies and an antibody to the CD40 antigen, which is a member of the tumor necrosis factor (TNF) receptor family, which is expressed on B-cells. Antibody therapy has been incorporated into CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) therapy and other regimens such as EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) and HyperCVAD (cyclophosphamide, vincristine, adriamycin, dexamethasone). Single-agent anti-CD20 therapy is active in the post-transplantation lymphoproliferative disorders. T-cell antibodies are under evaluation in a number of T-cell lymphoproliferative disorders. Targeted therapy has changed the natural history of a number of aggressive non-Hodgkin lymphomas. This review will describe the contributions of antibody therapies to the treatment of these diseases.

The aggressive lymphomas are potentially curable. The aggressive lymphomas include diffuse large B-cell lymphoma (DLBCL), mediastinal thymic large-cell lymphoma, intravascular large B-cell lymphoma, primary effusion lymphoma, Burkitt lymphoma, peripheral T-cell lymphoma, the immunodeficiency-associated lymphoproliferative disorders (lymphoproliferative diseases associated with primary immune disorders, and methotrexate-associated lymphoproliferative disorders), precursor B-lymphoblastic leukemia/lymphoma, and precursor T-lymphoblastic leukemia/lymphoma.

The identification of lymphoma-specific surface markers has lead to the development of monoclonal antibodies that target these antigens. Monoclonal antibodies, monoclonal antibodies conjugated to radioisotopes, and stem cell transplantation with these therapeutic modalities are incorporated into the management strategies with chemotherapy in the aggressive lymphomas. B-cell and T-cell antibodies are currently being evaluated in aggressive lymphomas.

The most widely studied therapeutic antibody is directed against a pan–B-cell antigen, CD20, which is not shed into the cytoplasm and does not internalize or undergo significant modulation.

DLBCL

Background
CHOP-21 (cyclophosphamide, adriamycin, vincristine, and prednisone administered every 21 days) therapy, which resulted in a 30% to 40% overall survival (OS) at 5 years, was the standard of care in DLBCL. The natural history of DLBCL, the most common aggressive lymphoma, has been altered by anti-CD20 monoclonal antibody therapy.

Rituximab—phase 2 studies
Rituximab is a chimeric anti-CD20 human immunoglobulin G1 monoclonal antibody approved for the treatment of DLBCL. Phase 2 studies of single-agent rituximab (Rituxan®, Genentech/Biogen-IDEC) combined with CHOP chemotherapy demonstrated feasibility and safety in a phase 2 study of single-agent anti-CD20 monoclonal antibody and in a phase 2 study of rituximab in combination with CHOP.
(R-CHOP) in previously untreated patients. These initial trials prompted a series of phase 3 studies, which are summarized in Table 1.

Rituximab: phase III trials in newly diagnosed elderly patients

Age is an important issue in the treatment of patients. Strategies were initiated in DLBCL that utilized the International Prognostic Factor Index (IPI), which is based on age as the primary strategy incorporating the age-adjusted IPI (aa-IPI). This is based on stage, serum lactate dehydrogenase, and performance score as stratification factors to design clinical trials.

GELA trial

In a landmark phase 3 trial of R-CHOP versus CHOP in previously untreated elderly patients, most of whom had DLBCL, the Groupe d’Etude des Lymphomes de l’Adulte (GELA) group reported superior progression-free survival (PFS) and OS with R-CHOP. In this study, rituximab was administered on day 1 of each of 8 CHOP cycles compared with CHOP. A total of 399 patients aged 60 to 80 years were randomized to receive 8 cycles of CHOP or R-CHOP. The event-free survival (EFS) \((P = .00002)\), PFS \((P < .0001)\), disease-free survival (DFS) \((P = .0003)\), and OS \((P = .007)\) were all in favor of the R-CHOP arm. Benefit was observed in both low-risk aa IPI and high-risk aa-IPI groups. The median PFS was 1.5 years for CHOP and not reached for R-CHOP, and the median OS was 3.1 years for CHOP and not reached for R-CHOP. Nearly half of the R-CHOP patients were event free compared with 28% in the CHOP arm. The 7-year PFS was 52% for R-CHOP and 29% for CHOP \((P < .0001)\), DFS, 66% for R-CHOP and 42% for CHOP \((P = .0001)\), and the OS 53% for R-CHOP and 36% for CHOP \((P = .0004)\). A total of 47% of patients died in the R-CHOP arm and 65% in the CHOP arm, with 71% and 80% of the respective deaths related to lymphoma or treatment toxicity. The 7-year survival curves for aa-IPI score 0 or 1 and aa-IPI score 2 or 3 for R-CHOP versus CHOP were 71% versus 49% \((P = .003)\) and 42% versus 28% \((P = .021)\), respectively.

Intergroup/ECOG trial

The US Intergroup Trial—Eastern Cooperative Oncology Group (ECOG) 4494/Cancer and Leukemia Group B (CALGB) 9793 trial with participation from the Southwest Oncology Group (SWOG)—was a prospective randomized phase 3 study comparing failure-free survival (FFS) in elderly patients with DLBCL assigned to either R-CHOP or CHOP followed by a second random assignment in responders to either maintenance rituximab (MR) or observation. This trial was designed to address the failure of induction therapy and failure to maintain a response. From February 1998 through July 2001, 46% of patients received 6 chemotherapy cycles and 33% received 7 or more cycles. In contrast to the GELA study, the number of rituximab infusions was 4 with 6 chemotherapy cycles and 5 with more than 6 cycles. With a median follow-up of 3.5 years, the estimated 2-year FFS rates after second random assignment were 77% for R-CHOP followed by observation, 79%

<table>
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Abbreviations: CR, complete remission; EFS, event-free survival; FFS, failure-free survival; OS, overall survival; NS, not significant; NA, not available

*secondary analysis; †both rituximab arms only; ‡for 6×R-CHOP-14 versus 6×CHOP-14
for R-CHOP + MR, 74% CHOP + MR, and 45% for CHOP followed by observation (P < .001). These findings suggested an additive rather than a synergistic effect of rituximab. A secondary analysis was performed to elucidate the effects of induction treatment without MR. In this analysis, R-CHOP alone significantly decreased the risk of treatment failure compared to CHOP alone (hazard ratio [HR] = 0.64; 95% confidence interval [CI], 0.47 to 0.85; P = .003) with an estimated 3-year FFS rate of 52% for R-CHOP and 39% for CHOP. In addition, OS was longer after R-CHOP induction alone (HR = 0.72; 95% CI 0.52 to 1.00; P = .05) with an estimated 3-year OS rate of 67% for R-CHOP and 58% for CHOP. There was a FFS benefit for R-CHOP in low/low-intermediate-risk and high intermediate/high-risk IPI patients (P < .03). In comparing the GELA and US Intergroup Trials, the 3-year FFS (R-CHOP, 53% and 52%; CHOP, 35% and 35%, respectively), OS (R-CHOP, 62% and 67%; CHOP, 51% and 58%, respectively) and respective FFS HR (0.58 and 0.64) and OS HR (0.72 and 0.72) were similar in the GELA and US Intergroup Trial despite differences in the percentages of trial patients with high-risk IPI scores (R-CHOP, 12% versus 23%; CHOP, 15% versus 27%, respectively). The continued use of maintenance rituximab after R-CHOP failed to demonstrate benefit at the time of the initial report and in follow-up at 5.5 years. The percentage of treatment failures within 2 years was 85% for the CHOP observation arm, and 61% in the CHOP maintenance arm (P = .013). The percentage of failure was 53% in the CHOP observation arm and 47% in the R-CHOP MR arm.

Canadian population study
A Canadian population study confirmed the OS observations of R-CHOP over CHOP from the GELA and the US Intergroup trials. A total of 292 patients with DLBCL treated in the province of British Columbia were retrospectively evaluated in a population-based analysis. Of these, 140 patients with a median follow-up of 42 months (range, 5 to 52 months) were treated in the pre-rituximab era with CHOP-like therapy, and 152 patients with a median follow-up of 24 months (range, 9 to 35 months) in the postrituximab era were treated with rituximab 24 to 72 hours after a CHOP infusion. The median age was 64 years (range, 10 to 86 years), and there were no differences in relevant clinical prognostic factors. More patients in the pre-rituximab group received radiation therapy (RT) compared with the post-rituximab group (24% vs 14%; P = 0.04). The risk ratio (relative risk [RR], 0.40; P < .002) and the OS (RR, 0.40, P < .001) were significantly improved in the post-rituximab group regardless of age.

Rituximab: phase 3 trials in newly diagnosed younger patients—the MinT trial
The MinT (Mabthera International Trial) study was a randomized international trial of 824 young patients with good-prognosis (favorable and intermediate-risk) DLBCL from 18 countries and 172 participating institutions. Patients received either 6 cycles of CHOP-like chemotherapy (CHOEP [CHOP plus etoposide]); MACOP-B (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, and bleomycin); and PMitCEBO (mitoxantrone, cyclophosphamide, etoposide, vincristine, bleomycin, and prednisone) plus rituximab (413 patients, 355 evaluable for response) or CHOP-like therapy (411 patients, 350 evaluable for response) alone with additional radiation therapy to bulky and extranodal disease. Patients had 0 or 1 adverse IPI risk factors, stage II to IV disease, or stage I disease with bulky disease. The primary endpoint was EFS with intention-to-treat analyses. There were 57 lymphoma-associated deaths in the chemotherapy-alone arm and 19 in the chemotherapy and rituximab arm. At a median follow-up of 34 months (range, 0.03-61), patients treated with chemotherapy and rituximab had an increased 3-year EFS of 79% (95% CI, 75-83) versus 59% (95% CI, 54-64) with chemotherapy alone with a difference between the groups of 20% (95% CI, 13-27), P < .0001 and an increased 3-year OS of 93% (95% CI, 90-95) versus 84% (95% CI, 80-88) with a difference between the groups of 9% (95% CI, 3-13), P = .0001. The most favorable outcomes were in patients with an IPI of 0 and no bulky disease with the 3-year EFS of 97% after 6 cycles of CHOP plus rituximab and 3-year OS of 98% after any chemotherapy and rituximab and 100% after 6 cycles of CHOP plus rituximab in patients with stage II disease. In the less favorable subgroups, patients had a 76% 3-year EFS after chemotherapy plus rituximab, with bulky disease being defined at different sites as 5 cm to 10 cm, with the majority being 7.5 cm; these patients had consolidative radiation therapy. In this study, nearly twice as many patients failed after chemotherapy compared with chemotherapy plus rituximab (41% vs 21%). There was no benefit to the addition of etoposide to R-CHOP.

Trials of rituximab and combination chemotherapy regimens of variable cycle length
Two studies have demonstrated that standard-dose CHOP administered every 14 days (CHOP-14) results in a longer OS than CHOP-21 in patients ages 18 to 60 and ages 61 to 75. Phase 2 studies evaluating R-CHOP-14 have been reported. The German High-Grade Lymphoma Study Group phase 3 study compared 14-day cycles of CHOP (CHOP-14) with 14-day cycles of R-CHOP. In multivariate analysis for OS adjusting for stratification variables, only the OS after 6 cycles of R-CHOP-14 (RR, 0.63; P = .003) was statistically significant. An international study conducted by the French GELA and British National Cancer Research Institute will further address the question of every-2-week versus every-3-week R-CHOP.

Unique reported toxicities of R-CHOP-14 therapy
Seven (14%) patients in a phase 2 study of 50 patients treated with R-CHOP-14 supported by pegfilgastrim developed interstitial pneumonitis, 4 of them at the end of therapy. No patient was neutropenic, and all had an ab-
normal high-resolution CT scan of the chest. The bronchoalveolar lavage revealed *Pneumocystis carinii* in 3 of 5 patients with CD4 counts of 168, 190, and 359/µL. A correlation with hypogammaglobulinemia was observed. Cotrimoxazole prophylaxis was recommended.18

**Trials of rituximab and other combination chemotherapy regimens**

The infusion regimen DA-EPOCH-R (dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, rituximab) has been developed at the U.S. National Cancer Institute (NCI), and preliminary data demonstrate that this regimen is effective among all biomarker subgroups.20 The CALGB has initiated a phase 3 randomized study of R-CHOP-21 versus DA-EPOCH-R incorporating molecular profiling and pharmacogenomics to determine if DA-EPOCH-R represents a treatment advance.

**Rituximab in salvage therapy and high-dose therapy regimens**

The standard of care after recurrence of DLBCL is salvage therapy followed by high-dose chemotherapy with stem-cell transplantation.21 In phase 2 trials, the addition of rituximab to salvage chemotherapy regimens may improve the overall response rate with ICE (ifosfamide, carboplatin, and etoposide) and DHAP (dexamethasone, high-dose cytarabine, and cisplatin).22,23 The US Intergroup study (S9704) is also assessing the role of HDT and autologous transplantation after 5 cycles of R-CHOP versus completing 8 total cycles of R-CHOP-21 and no transplantation in younger patients with high-intermediate or high-risk disease.

**Anti CD20-based radioimmunoconjugates**

Experience with radioimmunotherapy (RIT) in aggressive lymphoma is limited to patients with relapsed/refractory disease, patients who have relapsed after stem cell transplantation or patients who were not eligible for stem cell transplantation. One approach to enhancing the cytotoxic potential of monoclonal antibodies is to attach them to a radionuclide to form a radioimmunoconjugate. The use of a radioimmunoconjugate is referred to as RIT. RIT targets the radionucleotide to cells to which the antibody is bound, surrounding tumor cells and the local microenvironment. Currently, two drugs are registered in the US: ibritumomab tiuxetan (Zevalin; Biogen- IDEC) and tositumomab (Bexxar; GlaxoSmithKline).

Ibritumomab, a murine anti-CD20 antibody, is attached to tiuxetin, an MX-DTPA linker chelator, to form ibritumomab tiuxetan. Yttrium-90 (90Y) emits pure β and γ emitter with the therapeutic dose based on dosimetry. On day 1, 450 mg of cold tositumomab is administered followed by 5 mCi of 131I-tositumomab with dosimetry on day 1, within days 2 to 4, and within days 6 to 7 after the dose. A therapeutic dose calculated to deliver 75 CGy to the whole body is administered to patients with a platelet count of greater than 150,000 cells/mm³.

In a phase 1/2 trial of 90Y-ibritumomab tiuxetan, the overall response rate (ORR) was 43% in patients with intermediate-grade histology. In an analysis of these patients in long-term follow-up, 7 of 12 (58%) of patients with DLBCL had a response, with a median duration of response of 49.8 months (1.3–67.6+ months).25

In 104 elderly patients with relapsed/refractory DLBCL who were not candidates for stem cell transplantation, the ORR to 90Y-ibritumomab tiuxetan was 19% in patients who were previously treated with rituximab. The ORR was 52% in patients who failed induction therapy and 53% in patients who relapsed after a CR. The median PFS/OS 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 plus rituximab. Two patients died of cerebral hemorrhage associated with grade 4 thrombocytopenia; 43% of patients experienced grade 3 or 4 hematologic toxicities. Thrombocytopenia typically occurred 3 weeks after treatment, and recovery was nearly complete by week 9 of treatment. Platelet transfusions were required by 26.9% of patients. 131I-tositumomab has also been evaluated in patients who were not candidates for high-dose chemotherapy and stem cell transplantation. A total of 71 patients were treated with 131I-tositumomab in 5 studies with 4 median prior therapies (range, 1-11) and median age of 59 years. At a median follow-up of 19.4 months (range, 0.5–101), the CR rate was 25% with an ORR of 39%. The median duration of response was 20 months (lower limit 10.8, upper limit not reached). The median time-to-progression (TTP) was 4.3 months (3.2–10.2) for all patients and 20.2 months (lower limit, 12.4; upper limit not reached) with 5 patients in remission longer than 40 months.

RIT has been incorporated into induction therapy in certain high-risk patients. In a phase 2 trial of R-CHOP followed by 90Y-ibritumomab tiuxetan RIT in high-risk patients (aa-IPI 2 and 3), the intent-to-treat OS was 63% and EFS was 59%. All patients who received RIT remained relapse free at a median of 21 months.28

In a phase 1 and 2 study, high-dose 131I-tositumomab was combined with high-dose etoposide and cyclophosphamide followed by autologous transplantation with improved outcomes.29 Other studies are in progress.
**Epratuzumab**

Epratuzumab is a humanized monoclonal immunoglobulin G1 antibody directed against the B-cell–specific antigen CD22 that is expressed by pre-B cells and mature, normal B cells and is expressed in approximately 85% of DLBCL. Epratuzumab has been combined with R-CHOP-21 in the treatment of previously untreated DLBCL.32 In the initial feasibility study of 15 patients with DLBCL, the CR rate was 67% and the PR rate was 20%. The 1-year PFS and OS rates were 93% and 100%; 2-year PFS and OS rates were 86% and 86%. Grade 3 or 4 neutropenia rates were observed in 14 patients (93%) in 28 of 92 (30%) of treatment cycles, with 11 patients (73%) requiring dose reductions. The North Central Cancer Treatment Group (NCCTG) has opened an expanded phase 2 study to evaluate this regimen.

**Anti CD40 antibodies**

SGN-40 is a humanized antibody against CD40 which is a member of the tumor necrosis factor (TNF) receptor family and is widely expressed on B-cell malignancies. No immune responses to SGN-40 have been detected. Anti-CD40 antibody therapy has been evaluated in a phase 1 study.33 Eight patients with recurring DLBCL completed cycle 1 with an ORR of 37.5% (1 CR and 2 PR).

**New drugs and new combinations of drugs**

Bortezomib on days 1 and 4 in a dose escalation study (0.7, 1.0, and 1.3 mg/m²) was added to R-CHOP in 40 patients.34 The 2-year PFS was 72%. Toxicities included peripheral neuropathy in 55%, grade 4 neutropenia in 15%, and thrombocytopenia in 15%. Lenalidamide and mTOR agents active as a single agent in patients with relapsed/refractory disease are potential agents for combination immunochemotherapy.35,36

**Conclusions in DLBCL**

Clinical trials have demonstrated that the addition of rituximab to CHOP has improved the DFS, EFS, and OS and established R-CHOP as the standard of care in DLBCL. Day-1 administration is convenient. The data at this time do not support the use of maintenance rituximab in DLBCL after R-CHOP therapy. Toxicity data, efficacy, cost, the results of infusion studies, the addition of CD20-based radioimmunoconjugates, the addition of new antibodies, and new combinations of therapy will establish future directions in DLBCL.

**Primary Mediastinal Large B-cell Lymphoma**

Primary primary mediastinal large B-cell lymphoma (MLBCL) is a subtype of DLBCL with distinct clinical characteristics that include a mediastinal presentation in young women, unique pathologic features, and a specific molecular gene-expression signature that shares features with classic Hodgkin lymphoma.37 The 5-year OS in MLBCL patients younger than 65 years who were treated with CHOP-R was 81%, and the impact of rituximab was not determined.38 In a nonrandomized series in which 26 patients were treated with DA-EPOCH and 26 patients with DA-EPOCH-R, rituximab was associated with a significantly improved EFS ($P = .038$) and OS ($P = .023$).39

**Intravascular Large B-cell Lymphoma**

Intravascular large B-cell lymphoma is a rare lymphoma that characteristically involves the lung, skin, central nervous system, and the peripheral nerves. Anthracycline-based chemotherapy is associated with approximately a 60% initial response rate; however, with follow-up longer than 3 years, only 10% of patients were alive and disease-free.40 Single-agent rituximab therapy is active in this disease.41 In one retrospective analysis of 20 patients, the median survival was 26 months versus 6.5 months with rituximab regimens, and not reached versus 7 months with high-dose therapy.42

**Burkitt Lymphoma/Leukemia**

Burkitt lymphoma is a rare lymphoma. DA-EPOCH-R, which is adjusted by pharmacodynamics, was administered over 4 days for 6 cycles in HIV-negative patients (n = 13) and 3 to 6 cycles in HIV-positive patients (n = 6), resulted in a CR rate of 100% in 19 patients.43 At a median follow-up of 28 months, all patients were alive and in remission.

**Immunodeficiency-Associated Lymphoproliferative Disorders**

The immunodeficiency-associated lymphoproliferative disorders include diseases associated with primary immune disorders, HIV-related lymphomas, post-transplant lymphoproliferative disorders, and methotrexate-associated lymphoproliferative disorders.

**HIV-Related Lymphomas**

The survival of HIV-related lymphomas in patients treated with highly active antiretroviral therapy (HAART) now approaches that of HIV-negative patients.44 A prospective randomized (2:1) phase 3 trial was performed by the AIDS-Malignancy Consortium where patients received 375 mg/m² of rituximab with CHOP (n = 99) or no immunotherapy (n = 50).45 After the achievement of a CR, the R-CHOP patients also received monthly doses of rituximab for 3 months (to a maximum dosage of 9 to 11 doses of antibody). All patients were also treated with HAART, filgrastim, and $P$ carinii prophylaxis. A total of 82% of patients had DLBCL in the R-CHOP arm, and 74% had DLBCL in the CHOP arm. At a median follow-up of 137 weeks, the TTP, PFS, and OS times for R-CHOP were 85, 38, and 110 weeks versus 125, 45, and 139 weeks for CHOP, respectively ($P$ = not significant, all comparisons). The progression rate was significantly higher in the CHOP arm (19% versus 7%; $P < .01$). Treatment-related infectious deaths were 14% with R-CHOP versus 2% with CHOP ($P = .035$) with 60% of patients with a CD4 count of less than 50/mm³. Six of the 15 deaths occurred during the maintenance phase of rituximab
treatment. Grade 3 or 4 neutropenia occurred in 39% of patients in the R-CHOP arm and 17% in the CHOP arm (P = .012). In this group of patients with AIDS, the reduction in the risk of lymphoma progression with rituximab treatment was offset by an increased risk of infectious death.

A pooled series of three prospective phase 2 trials that included the Italian Cooperative Group on AIDS and Tumors, the Division of Hematology at Vienna University, and the Albert Einstein Cancer Center in New York had nearly identical eligibility criteria and treatment plans evaluating rituximab in combination with a 96-hour infusion of CDE (cyclophosphamide, doxorubicin, and etoposide), plus granulocyte-colony-stimulating factor (G-CSF).46 Patients were treated with rituximab at a dose of 375 mg/m² intravenously on day 1 of each cycle followed by a 96-hour continuous infusion of cyclophosphamide 187.5 mg/m² per day, doxorubicin 12.5 mg/m² per day, and etoposide 69 mg/m² per day every 4 weeks up to 6 cycles. A total of 56 of the 74 patients received HAART therapy, and the CR rate was 70% (95% CI, 59%-81%), the estimated 2-year FFS, 59% (95% CI, 47%-71%), and the OS rate, 64% (95% CI, 52%-76%). Ten (14%) patients had opportunistic infections during or within 3 months of R-CDE and 17 (23%) developed non-opportunistic infections after 3 months of treatment. Infection was the cause of death in 6 (8%) of patients with 2 (3%) secondary to bacterial sepsis during R-CDE. Four (5%) were opportunistic infections that occurred between 2 and 8 months after R-CDE therapy. Again, the lower risk of progression was offset by early and late infection-related deaths. In patients with higher CD4 counts, the benefit may outweigh the risk, but this has not been confirmed in the post-HAART era in a prospective, randomized trial. The AIDS Malignancy Consortium is completing a randomized phase 2 trial of R-EPOCH.

Post-Transplantation Lymphoproliferative Disorders

The most common post-transplantation lymphoproliferative disorder (PTLD) is a monoclonal DLBCL, which is highly associated with immunosuppressive treatment and Epstein Barr virus (EBV). The treatment of PTLD includes local therapy, reduction of immunosuppression, monoclonal antibody therapy, and immune and cell-based therapies. In contrast to other lymphomas, patients may be in long-term remission following immunosuppression reduction and single-agent rituximab in PTLD. In 1999, Milped and colleagues reported a retrospective analysis of 32 patients treated with rituximab at a dose of 375 mg/m².47 The immunosuppression regimen was reduced in 27 of 32 patients. Rituximab was used as front-line therapy in 30 patients and as salvage in 2 patients. The ORR was 69% (CR, 20; PR, 2). At a median of 10 months, 4 patients relapsed. Other reports have followed.48,49 In a retrospective analysis, the major impact was on early response with a significant relapse rate, but in multivariate analysis rituximab treatment was associated with improved OS (P = .03) in CD20+ PTLD.49 Phase 2 data support these observations. Rituximab therapy after immunosuppressive reduction has resulted in ORR of 44 to 75% and CRs of 35 to 69%. The variable response rates relate to whether or not the PTLD was early or late, presence of EBV in the tissue, LDH level, type of organ transplantation, other comorbid conditions, histology variables, retrospective versus prospective studies and duration of follow-up.48,49 In a phase 2 study, the ORR was 44%, with a CR rate of 35% with few relapses where 65% of patients had delayed onset PTLD, likely accounting for the lower response rate.50

Antibody Therapy in T-Cell Lymphoma

Approximately 15% of NHL are T cell in origin.51 Clinically, T-cell lymphomas are extranodal (cutaneous and non-cutaneous), nodal, and leukemic. Current immunotherapeutic approaches include antibodies directed against the T-cell proteins that include CD2, CD4, CD30, CD52, and CCR4.

Denileukin difitox

Denileukin difitox was the first targeted therapy approved by the US Food and Drug Administration (FDA) in cutaneous T-cell lymphomas. Denileukin difitox targets the intermediate- and high-affinity interleukin (IL)–2 receptor. Relapsed and refractory patients with CD25+CD25– with aggressive peripheral T-cell lymphoma (PTCL) were treated with a dose of 18 µg/kg/d.52 A total of 48% of patients responded, with a CR in 5 patients. The PFS was 6 months with several patients experiencing a 2-year PFS. There was not a correlation between patient response and CD25 expression. A phase 2 trial of CHOP and denileukin difitox in aggressive T-cell lymphoma is ongoing.

Alemtuzumab

A 36% response rate has been reported in refractory PTCL in patients treated with single-agent alemtuzumab, a humanized anti-CD52 monoclonal antibody.53 Patients were treated with 30 mg intravenously 3 times per week for a maximum of 12 weeks after an escalating dose over the first week. All patients received trimethoprim/sulfamethoxazole and valacyclovir prophylaxis. Three of 14 patients achieved a CR (2, 6, and 12 months in duration). In contrast to other lymphomas, patients may be in long-term remission following immunosuppression reduction and single-agent rituximab in PTLD. In 1999, Milped and colleagues reported a retrospective analysis of 32 patients treated with rituximab at a dose of 375 mg/m².47 The immunosuppression regimen was reduced in 27 of 32 patients. Rituximab was used as front-line therapy in 30 patients and as salvage in 2 patients. The ORR was 69% (CR, 20; PR, 2). At a median of 10 months, 4 patients relapsed. Other reports have followed.48,49 In a retrospective analysis, the major impact was on early response with a significant relapse rate, but in multivariate analysis rituximab treatment was associated with improved OS (P = .03) in CD20+ PTLD.49 Phase 2 data support these observations. Rituximab therapy after immunosuppressive reduction has resulted in ORR of 44 to 75% and CRs of 35 to 69%. The variable response rates relate to whether or not the PTLD was early or late, presence of EBV in the tissue, LDH level, type of organ transplantation, other comorbid conditions, histology variables, retrospective versus prospective studies and duration of follow-up.48,49 In a phase 2 study, the ORR was 44%, with a CR rate of 35% with few relapses where 65% of patients had delayed onset PTLD, likely accounting for the lower response rate.50

Antibody Therapy in T-Cell Lymphoma

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evaluated in phase 1 and 2 trials in additional CD2+ lymphoproliferative disorders.

Conclusion
Targeted therapies with monoclonal antibodies and monoclonal antibodies conjugated to radioimmunoconjugates have altered the natural history and the approach to treatment of aggressive non-Hodgkin lymphomas.

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References
31. Winter JN, Inwards DJ, Spies S, et al. 90Y ibritumomab tiuxetan (Zevalin); (90Y) doses higher than .4 mCi/kg may be safely combined with high-dose BEAM and autotransplant: the role of dosimetry [abstract]. Blood. 2004;104:329a.