Biologic Agents in the Management of Hodgkin Lymphoma

Armin Rashidi, MD, PhD, and Nancy L. Bartlett, MD

Abstract

The advent of biologic approaches for the treatment of solid tumors and hematologic malignancies has been a major accomplishment in oncology and a rapidly growing field of clinical and translational research in cancer therapeutics. Classical Hodgkin lymphoma (HL) is no exception. Although the investigation of biologic therapies in HL started decades ago, it has only recently flourished, largely because of the development of new monoclonal antibody drug conjugates and checkpoint inhibitors. Biologic therapies represent a potent treatment option that have produced durable remissions even in patients who have had multiple relapses or with refractory disease. This article reviews 8 major classes of biologic approaches that have been investigated in HL: monoclonal antibodies, immunotoxins, antibody-drug conjugates, radioimmunotherapy, adoptive immunotherapy, immunomodulators, chimeric antigen receptor T cells, and checkpoint inhibitors. An armamentarium of biologic therapies for HL that are well tolerated and potentially more effective is expected to be available in the near future. (J Natl Compr Canc Netw 2015;13:587–596)

Monoclonal Antibodies

Anti-CD30 Monoclonal Antibodies: SGN-30 and MDX-060

CD30, a member of the tumor necrosis factor α (TNF-α) superfamily, is highly expressed by Hodgkin Reed-Sternberg (HRS) cells,1,2 with very low expression levels on normal cells. In a phase II study, 38 patients with relapsed/refractory HL with a median of 3 prior therapies were treated with SGN-30, a chimeric monoclonal antibody constructed from an anti-CD30 murine antibody and the human gamma-1 heavy chain and kappa light chain constant regions.3 No responses were observed in this study, although 29% of patients had stable disease (SD).4

MDX-060, another human anti-CD30 monoclonal antibody, also showed a disappointing overall response rate (ORR) of 25%.5 Other attempts to design more effective anti-CD30 molecules were similarly disappointing; examples include MDX-14016 and XmAb2513.7 Although the monoclonal anti-CD30 antibodies are inactive as single agents in HL, they serve as the critical backbone of the anti-CD30 antibody drug conjugate, brentuximab vedotin, as discussed herein.

Most patients with newly diagnosed classical Hodgkin lymphoma (HL) have an excellent prognosis after multiagent chemotherapy with or without radiation. Biologic agents offer highly desirable approaches to patients with relapsed or refractory disease in which the use of more chemotherapy may be limited by intrinsic disease chemorefractoriness or residual side effects from prior therapies. This article discusses different biologic approaches to the treatment of HL. Although allogeneic stem cell transplantation (allo-SCT) represents a potent biologic therapy because of its graft-versus-lymphoma effect, allo-SCT alone as a regimen will not be discussed in this article.
Anti-CD20 Monoclonal Antibody: Rituximab

Although neoplastic cells express CD20 in only 20% to 30% of patients with HL,8–10 rituximab (an anti-CD20 monoclonal antibody) has documented activity in HL, even those with CD20-negative malignant cells. The effects of rituximab are postulated to be related to (1) elimination of nonmalignant CD20-positive B cells from the microenvironment, which may provide support for HRS cells and protect them against immune response, (2) killing the HRS stem cells which have a memory B-cell phenotype with CD20 expression,11 and (3) elimination of the infrequent CD20-positive HRS cells.

In 2003, Younes et al12 reported responses to single-agent rituximab in 5 of 22 patients with relapsed classical HL. Responses occurred in patients lacking expression of CD20 on HRS cells. Subsequent studies examined combinations of rituximab with chemotherapy. In a phase II study of 33 patients with relapsed HL, a combination of gemcitabine and rituximab resulted in an ORR of 48%,13 in contrast to single-agent studies with gemcitabine, which have yielded response rates of 20% to 40%.14,15 Rituximab with gemcitabine, ifosfamide, and oxaliplatin yielded an ORR of 86% and a complete response (CR) rate of 76% in 21 patients with relapsed/refractory HL.16 Because of the favorable toxicity profile and modest activity seen in relapsed disease, rituximab was combined with ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) in the frontline therapy of HL. In a phase II study of 49 patients with untreated stage II–IV HL (8% CD20-positive), 8 doses of rituximab (weekly for 5 doses, then day 1 of cycles 2, 4, and 6) in combination with standard ABVD resulted in a CR rate of 81%, 3-year progression-free survival (PFS) rate of 83%, and 3-year overall survival (OS) rate of 98%.17 In a larger phase II study of 78 patients with untreated bulky stage II or stage III–IV HL, 6 weekly doses of rituximab in combination with ABVD resulted in rates of 5-year event-free survival (EFS) and OS of 83% and 96%, respectively.18 Whether these results represent an improvement over the 5-year failure-free survival of 74% reported with ABVD alone in a recent phase III study is unclear.19 Results of a multicenter randomized phase II study (ClinicalTrials.gov identifier: NCT00654732) comparing rituximab-ABVD and ABVD for advanced-stage HL are pending, although the study was closed early because of low accrual and will likely provide underpowered comparisons.

The only phase III study evaluating the addition of rituximab to standard chemotherapy for HL was conducted by the German Hodgkin Study Group.20 Patients with newly diagnosed HL (stage IIB or III–IV) were treated with 2 cycles of BEACOPPesc (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by a PET scan. Patients with negative PET results were randomized to an additional 2 versus 6 cycles of therapy. The 439 patients with positive PET results were randomized to 6 more cycles of BEACOPPesc versus rituximab-BEACOPPesc. Grade 4 toxicity (most commonly leukopenia) developed in more than 90% of patients in both groups. The 3-year OS and PFS rates were not different between the groups (>90% in both). Despite interesting preclinical data suggesting a potential role for rituximab in HL, the addition of rituximab to standard regimens for HL is not recommended outside the setting of a clinical trial.

Nodular lymphocyte-predominant HL (NLPHL) is a rare CD20-positive subtype of HL. Accordingly, rituximab is an effective treatment in this disease, both in untreated and relapsed cases. Four weekly doses of rituximab in patients with relapsed NLPHL resulted in an ORR of 94% (n=15), with a median time to progression (TTP) of 33 months.21 In a study of 39 patients with NLPHL (21 treatment-naive), 4 weekly doses of rituximab resulted in 100% ORR (CR 67%), with no difference between patients treated as frontline or after relapse.22 A total of 16 patients in this study received maintenance rituximab (4 weekly doses every 6 months for 2 years). No difference was seen in outcomes between patients who received maintenance rituximab and those who did not, although a nonsignificant trend was seen toward longer TTP in the maintenance group. Relapse occurred in 59% of patients, and unexpectedly, 39% of these patients showed transformation to aggressive lymphoma at the time of relapse. Currently, local radiation is the standard treatment for early-stage NLPHL. For patients with stage III/IV disease, combination chemotherapy or rituximab in combination with chemotherapy is the preferred approach. Importantly, both at initial diagnosis and relapse, some patients are asymptomatic, with minimal dis-
Biologics in Hodgkin Lymphoma

These results discouraged the use of this agent in larger studies.

Anti-CD80 Monoclonal Antibodies: Galiximab
Galiximab is a primatized monoclonal antibody against CD80, which is a costimulatory molecule expressed on HRS cells and associated with proliferation of background T cells. In a phase II study of 29 patients with heavily pretreated relapsed HL, single-agent galiximab (4 weekly doses of 500 mg/m² followed by monthly injections until disease progression) showed minimal activity, with an ORR of only 10% and a median PFS of 1.6 months. Development of this drug was discontinued in 2010.

Antibody-Drug Conjugates and Immunotoxins
Antibody-drug conjugates (ADCs) consist of an antibody targeting neoplastic cells coupled with a cytotoxic agent, whereas immunotoxins generally refer to agents that combine an antibody and a biologic toxin. This section reviews 1 ADC and 2 immunotoxins relevant to the treatment of HL.

Anti-CD30 ADC: Brentuximab Vedotin (SGN-35)
Brentuximab vedotin (BV) is an ADC consisting of the chimeric monoclonal antibody targeting CD30 (brentuximab), linked to the microtubule disrupting agent monomethyl auristatin E (MMAE; vedotin). Binding of MMAE to tubulin disrupts the microtubule network, resulting in cell cycle arrest and apoptosis of the CD30-expressing tumor cells. BV is currently the single most active biologic agent for the treatment of HL and the focus of several studies described herein.

Subsequent to 2 phase I dose escalation studies, a large pivotal phase II study demonstrated the safety and activity of BV in relapsed/refractory HL. In this multicenter clinical trial, 102 patients with relapsed/refractory HL after autologous stem cell transplant (auto-SCT) were treated with 1.8 mg/kg of BV every 3 weeks for up to 16 cycles. An impressive ORR of 75% (including a 34% CR rate) was achieved. The median duration of response in patients who achieved a CR was 20 months, and the median PFS for all patients was 5.6 months (21.7 months for those who achieved a CR). The most common adverse event was peripheral sensory neuropathy (42%) and the most common grade 3 to 4 adverse event was neutropenia (20%). In 2011, BV was granted accelerated approval by the FDA for the treatment of patients with HL after failure of auto-SCT or at least 2 prior multiagent chemotherapy regimens (if transplant-ineligible).

Two rare adverse events associated with BV warrant special attention. The first is progressive multifocal leukoencephalopathy. This frequently life-threatening JC virus–induced central nervous system infection has been reported in 5 patients treated with BV after 2 to 6 doses. It has been suggested that anti–JC virus immune surveillance is impaired in patients treated with BV because of the depletion of CD30-expressing activated T cells. The other rare but potentially fatal side effect of BV is acute pancreatitis. This complication also occurs early in the course of treatment, typically by the third cycle, and potential mechanisms include unintended targeting of low-level pancreatic CD30 and toxicity from free MMAE.

The use of BV has been studied both before and after allo-SCT. A retrospective analysis of 18 patients who underwent reduced-intensity allo-SCT after treatment with BV for relapsed/refractory HL and a subsequent follow-up report (n=21) showed a 2-year PFS rate of 59% in the BV group compared with 26% for a historical control group not receiving BV before transplant. Unfortunately, no evidence of a plateau was seen in the PFS curve. With a median follow-up of 30 months, the 1- and 3-year nonrelapse mortality rates among patients treated with BV were 9.5% and approximately 35%, respectively. The incidence of graft-versus-host disease did not exceed historical rates in allo-SCT performed for other hematologic malignancies. Although these results suggested the feasibility of allo-SCT after treatment with BV, no definitive conclusions can...
be drawn because of the retrospective nature of the comparison.

Another phase II study included patients with HL experiencing relapse after allo-SCT. Treatment with BV resulted in an ORR of 50% (38% CR) and a median PFS of 7.8 months. The median OS was not reached after a median follow-up of 34 weeks. Fever occurred in 52% of patients. Other side effects were as expected based on other studies, and included peripheral sensory neuropathy (48%) and grade 3 to 4 neutropenia (24%). The results of this study suggested that BV is a viable treatment option in the particularly challenging setting of relapse after allo-SCT.

Results were recently published of the randomized, double-blind, placebo-controlled, multicenter phase III AETHERA study (ClinicalTrials.gov identifier: NCT01100502), evaluating BV as consolidation therapy after auto-SCT in high-risk patients. Patients had primary refractory disease, or experienced disease relapse either less than 12 months after frontline therapy or 12 or more months after frontline therapy with extranodal disease. After auto-SCT, they were randomized to BV consolidation (1.8 mg/kg every 3 weeks) versus placebo for up to 16 cycles. The primary end point of the study was PFS. A total of 329 patients were enrolled. Crossover was allowed for patients who experienced progressive disease on the placebo arm.

Approximately 55% of patients in each group had received 1 prior salvage therapy and the remainder had received 2 or more. Approximately half of the patients in each group completed the planned treatment, with a median of 15 cycles in both groups. Adverse events resulting in dose reduction occurred in 32% and 3% of the BV and placebo groups, respectively. Progressive disease occurred in 15% and 42% of patients, respectively, and was the most common reason for treatment discontinuation among patients who did not complete the planned number of cycles of treatment. Consolidation resulted in significantly improved 2-year PFS assessed by an independent review facility (63% vs 51% with placebo; hazard ratio, 0.57; P=.001), with consistent benefit across most subgroups. The PFS was not significantly different between the groups when analysis was limited to those with negative PET results before auto-SCT, relapse more than 12 months after frontline therapy, or CR after salvage therapy before auto-SCT. The lack of statistical significance in these subgroups may have been related to small numbers. Importantly, no difference was seen in OS between the BV and placebo groups, which may be explained by the allowance for crossover and subsequent salvage therapies in patients in the placebo group. Peripheral sensory neuropathy occurred in 56% of patients in the BV arm (grade 3 in 10%, grade 4 in 0%), and was manageable with dose reductions, dose delays, or no intervention in 66% of such cases. Neutropenia was the second most common adverse event, occurring in 35% of patients in the BV arm (grade 3 or higher in 29%). These results demonstrated that consolidation BV is reasonable after auto-SCT in high-risk patients. The role of BV after auto-SCT needs to be defined in patients with prognostic factors, specifically long first remission durations and negative PET results before auto-SCT. Similarly, the results of this study may not be applicable to patients who had previous treatment with BV.

Although BV is not currently approved for first salvage therapy in HL before auto-SCT, several studies are underway investigating its use in this setting. Interim results of a phase I/II study (ClinicalTrials.gov identifier: NCT01874054) of BV in combination with bendamustine in patients with first relapse or primary refractory HL showed excellent tolerability and activity. This trial has enrolled 54 patients (50% with primary refractory disease). No dose-limiting toxicity was observed in cycle 1, and the dose of bendamustine for combination with standard-dose BV was selected at 90 mg/m² (days 1 and 2 every 3 weeks). The main toxicities were infusion-related reactions, which occurred within 24 hours of cycle 2 infusion, and were effectively reduced using premedication with steroids and antihistamines. CR and ORR rates of 83% and 96% were achieved, respectively, with most CRs occurring after 2 cycles. The median duration of response and PFS were not reached at the time of presentation. Stem cell mobilization/collection was adequate in all 31 patients who underwent auto-SCT.

The use of BV as a single agent for first-line salvage therapy before auto-SCT is also being explored. In an ongoing phase II multicenter study (ClinicalTrials.gov identifier: NCT01393717), patients received BV (1.8 mg/kg every 3 weeks) for 2 cycles, followed by a PET scan. Those with progressive disease received an alternative salvage therapy followed
by auto-SCT, whereas all other patients received 2 more cycles of BV followed by a second PET scan. According to the second interim PET scan, patients with at least a partial response proceeded with auto-SCT. The primary end point for this study was ORR, and 36 patients were evaluable. An ORR of 69% (CR 36%) was obtained, whereas progressive disease occurred in 3%. No growth factor support or transfusions were required. Peripheral neuropathy was the most common adverse event, occurring in 52% of patients. A total of 89% of patients proceeded to auto-SCT and 1 patient received an allo-SCT. BV was the only salvage therapy before transplant in 52% of patients. Stem cell mobilization and engraftment were not adversely affected. An amendment was made based on these results to increase the dose of BV to 2.4 mg/kg for patients not achieving a CR with the first 2 cycles.

In another study,^{43} 2 cycles of BV (1.2 mg/kg weekly for 3 weeks on and 1 week off) were administered before an interim PET scan. Patients with negative PET results proceeded to auto-SCT, whereas other patients received 2 cycles of augmented ICE (ifosfamide, carboplatin, and etoposide) before auto-SCT. A total of 46 patients were enrolled (45 evaluable for the primary end point); 27% of patients received negative PET results after BV and proceeded to auto-SCT, and 69% of the remaining patients received negative PET results after augmented ICE and proceeded to auto-SCT. Of the 28 patients who reached day 90 posttransplant, 75% had primary refractory disease or relapse within 1 year of frontline therapy. Ten patients had persistent disease after BV and augmented ICE. All of these patients eventually received auto-SCT: 3 without additional therapy, 3 after achieving a CR with radiation, 3 after achieving a partial response with radiation, and 1 after a third cycle of augmented ICE. With a median follow-up of 20.1 months posttransplant, the 2-year OS and EFS rates were 95% and 80%, respectively. The 2-year EFS rates were 92% for patients with negative PET results after BV alone and 91% for those with negative PET results after BV and augmented ICE. For patients with positive PET results after salvage therapy, the 2-year EFS rate was 46%. One patient died with progressive multifocal leukoencephalopathy 7 months posttransplant. The optimal approach for incorporating BV into first-line salvage should be studied in randomized trials.

Several ongoing phase II studies in both early- and advanced-stage disease are exploring frontline combinations with BV either sequentially or concurrently. The first published report of BV as initial treatment for HL was a phase I dose escalation study, in which BV was used in combination with ABVD in patients with bulky stage IIA or stage IIB–IV disease.^{44} BV was given on days 1 and 15 with standard-dose ABVD. Growth factor support was instituted for the treatment of grade 3 or higher neutropenia, and as prophylaxis in subsequent cycles. The maximum planned dose of BV was 1.2 mg/kg per dose, and this was well tolerated. Of 25 patients, 11 (44%) developed pulmonary toxicity after cycles 3 to 6, with 2 treatment-related deaths. The protocol was then amended to eliminate bleomycin from the regimen, and an additional 26 patients were treated with BV-AVD with no pulmonary toxicity.^{45} CR rates of 95% and 96% were achieved in the BV-ABVD and BV-AVD cohorts, respectively. The 3-year failure-free survival rates were 83% and 96%, respectively. The corresponding rates for 3-year OS were 92% and 100%, respectively. The incidence of febrile neutropenia was 20% and 8% in the 2 cohorts, respectively. The phase I regimen served as the basis for the currently active phase III ECHELON-1 clinical trial (ClinicalTrials.gov identifier: NCT01712490) comparing frontline BV-AVD to ABVD in patients with advanced-stage HL. Accrual to this 1000-patient study is expected to be complete in late 2015 or 2016. Incorporation of BV into frontline therapy is not recommended outside the setting of a clinical trial.

Interim results of a phase II study (ClinicalTrials.gov identifier: NCT01716806) of frontline BV (alone or in combination with bendamustine or dacarbazine) in patients with HL older than 60 years showed that with single-agent BV (n=27), the CR rate and ORR were 70% and 93%, respectively, and the median PFS for those with a CR was 8.7 months.^{46} The short median PFS suggests BV alone is inadequate as frontline therapy. Peripheral sensory neuropathy was the most frequent side effect in this arm, with 22% of patients developing grade 3 or higher sensory neuropathy. High response rates were also reported for a small cohort treated with BV and dacarbazine, but remission duration was not described.

**Anti-CD25 Ricin A-Chain Immunotoxin:**

**RFT5-dgA and Ki-4.dgA**

RFT5.dgA and Ki-4.dgA are immunotoxins constructed by linking the monoclonal antibodies RFT5 (anti-CD25) and Ki-4 (anti-CD30) to the toxin de-glycosylated ricin A-chain (dgA). The use of these...
compounds was based on the frequent expression of CD25 and CD30 on HRS cells. The largest phase I/II studies of these immunotoxins were performed on 27 and 17 patients, respectively, with relapsed/refractory HL.\(^{47}\) Capillary leak syndrome was the main dose-limiting toxicity in both groups. In the group treated with RFT5.dgA, the ORR rate was 15%, whereas 27% of patients had SD. In the group treated with Ki-4.dgA, the rates of ORR and SD were both 13%. Because of low response rates and high toxicity, these agents were not explored further.

**Anti-Tac(Fv)-PE38 (LMB-2)**

Anti-Tac(Fv)-PE38 (LMB-2) is an anti-CD25 recombinant immunotoxin that contains an antibody Fv fragment fused to a truncated form of the *Pseudomonas* exotoxin PE38. A phase I dose-escalation study was performed using LMB-2 in patients with CD25-positive hematologic malignancies, including 11 patients with relapsed/refractory HL.\(^{48}\) A total of 3 patients experienced a response (no CR), and 6 had SD.

**Radioimmunotherapy**

Radioimmunotherapy involves a combination of a radioisotope and an immunoglobulin with affinity to tumor cells. The immunoglobulin delivers the cytotoxic radioisotope to the tumor, and this approach can in fact be considered as targeted radiotherapy, rather than immunotherapy. The rationale behind this approach is the exquisite radiosensitivity of HL.

**Radiolabeled Antiferritin**

Thymus-derived lymphocytes in the tumor microenvironment synthesize and secrete ferritin.\(^{49,50}\) Because ferritin is not a membrane-bound compound, the radioimmunoconjugate agent binds to the interstitial ferritin within the tumor microenvironment, and does not result in antibody- or complement-mediated cytotoxicity. The largest phase II study of \(^{131}\)I-labeled antiferritin in patients with relapsed HL showed a 40% ORR among 37 patients;\(^{51}\) 1 patient achieved a CR. The results with Yttrium-90–labeled antiferritin in 39 patients with heavily pretreated relapsed/refractory HL showed a 51% ORR and a median OS of 6 months.\(^{52}\)

Radiolabeled antiferritin only targets lesions larger than 1 cm in diameter. Subcentimeter lesions have suboptimal neovascularization (required for adequate drug delivery), lack adequate ferritin, and tend toward same-site recurrence. As a result, it has been suggested that radiolabeled antiferritin be used before chemotherapy or external-beam radiation, because these modalities may decrease ferritin concentration in the tumor and detract from the effectiveness of radiolabeled antiferritin therapy.\(^{53}\) With the development of newer biologic therapies, further investigation of radiolabeled antiferritin is not currently being pursued.

**131I-radiolabeled Anti-CD25 Conjugate: CHT-25**

CHT-25 is a \(^{131}\)I-radiolabeled anti-CD25 conjugate. HRS cells frequently express CD25.\(^{54,55}\) A phase I study using this drug in 11 patients with relapsed/refractory HL resulted in an ORR of 45% (2 CR).\(^{56}\) The authors are not aware of any other studies evaluating this agent.

**Radiolabelled Anti-CD30 Antibody: \(^{131}\)I-Ki-4**

\(^{131}\)I-Ki-4 is a radioimmunoconjugate consisting of a murine anti-CD30 monoclonal antibody and radioisotope \(^{131}\)I. In a study of 22 patients with relapsed/refractory CD30-positive HL, treatment with \(^{131}\)I-Ki-4 resulted in a 27% ORR (1 CR), with a median response duration of 4 months.\(^{57}\) Grade 4 hematologic toxicity developed in 32% of patients, discouraging further investigation of this agent.

**Adoptive Immunotherapy: Epstein-Barr Virus–Targeted Cytotoxic T-Cells**

HRS cells express Epstein-Barr virus (EBV)–associated antigens in approximately 40% of patients.\(^{58,59}\) Inspired by this observation, adoptive transfer of cytotoxic T cells (CTLs) with EBV antigen–specificity has been explored as a therapy for EBV-positive HL.\(^{60}\) In one study, 14 patients with EBV-positive, relapsed/refractory HL were treated with latent membrane protein 2 (LMP2)–specific autologous CTLs.\(^{61}\) These cells expanded up to 100-fold in vivo, persisted in the circulation as memory T cells, and trafficked to the tumor sites. Treatment was well tolerated and resulted in an ORR of 27% (including 2 patients with CR). Another 45% of patients had SD. Responses were limited and transient, especially in patients with bulky disease.

In another phase I study, alloreactive EBV-specific CTLs from unrelated donors or siblings were used to treat 6 patients with EBV-positive, relapsed/refractory HL.\(^{62}\) This approach was chosen to avoid
the potential defects in effector functions of autologous CTLs. Treatment was well tolerated and not associated with graft-versus-host disease. Three patients received fludarabine before CTL infusion. Two patients in the CTL-only cohort showed a transient partial response, whereas 1 patient experienced a durable partial response with no evidence of disease progression after 22 months of follow-up. In the fludarabine cohort, 2 patients had a partial response and 1 had SD for 7 months before progression. Investigation of EBV-specific CTL therapy for HL has been slowly evolving for nearly 2 decades, but whether a viable commercial product will become available is not clear.

**Immunomodulators: Lenalidomide**

Lenalidomide is an immunomodulatory drug with several different mechanisms of action. Importantly, lenalidomide alters the microenvironment and may affect the immunosuppressive milieu in which HRS cells reside. The efficacy of lenalidomide as a single agent in patients with relapsed/refractory HL was investigated in a pilot German study with 42 patients. The drug was given at a dose of 25 mg/d on days 1 to 21 of each 28-day cycle, and continued until disease relapse or unacceptable toxicity. No grade 3 to 4 toxicity was observed among the 31 evaluable patients. An ORR of 29% (1 CR) was achieved. These encouraging results led to a subsequent multicenter phase II study (ClinicalTrials.gov identifier: NCT00540007). Dosing and schedule were similar to the German study. Of the 38 enrolled patients with a median of 4 prior therapies (including auto- or allo-SCT in 87% and refractory disease in 55% of patients), 36 were evaluable for the primary end point (ORR). An objective ORR of 19% (1 CR) was achieved and an additional 14% of patients had SD. Response was associated with decreased levels of chemokines CCL17 and CCL22 at 2 weeks, suggesting the potential value of these chemokines as biomarkers for response. CCL17 is known to be highly expressed by HRS cells. In addition, serum levels of CCL17 and CCL22 are elevated in patients with HL compared with healthy controls. The median duration of response in this series was 6 months. The most common grade 3 to 4 adverse events were neutropenia (47%), anemia (29%), and thrombocytopenia (18%). The development of skin rash, hepatotoxicity, and cytopenia led to treatment discontinuation in 4 patients. Several studies are currently investigating lenalidomide in combination with other chemotherapy or targeted agents, or as maintenance after auto-SCT.

**Chimeric Antigen Receptor T Cells**

Because EBV-associated antigens on HRS cells are only weakly immunogenic and frequently lost during therapy, adoptive transfer of EBV-specific CTLs was associated with limited success. As a result, a CD30ζ chimeric antigen receptor (CAR) was constructed using the CD30-specific single-chain Fv fragment and the transmembrane and cytoplasmic domain of the T-cell receptor ζ chain. This construct was then cloned in a retroviral backbone and used to make CD30CAR EBV-specific CTLs. Two studies using this approach are actively recruiting patients (ClinicalTrials.gov identifiers: NCT01316146 and NCT01192464).

**Checkpoint Inhibitors: Nivolumab and Pembrolizumab**

T-cell exhaustion due to continuous antigen exposure is one of the immune escape mechanisms in many cancers. Programmed death-1 (PD-1) is a checkpoint receptor expressed on activated T cells, macrophages, and natural killer cells. Interaction between PD-1 and its ligands PD-L1/PD-L2, which are expressed on normal cells, leads to anergy and apoptosis of the effector cells. In the cancer setting, antigen-presenting cells continuously express PD-L1, which via interaction with PD-1 on natural killer and T cells, results in impaired immunity and reduced antitumor response. The same interaction also leads to expansion of regulatory T cells, which in turn impairs antitumor immunity. Similarly, PD-L1 expression is upregulated on tumor cell surfaces, presumably in response to the host immune system attempting to attack the tumor. This effect is mediated to a large extent by interferon γ. The outcome of PD-1/PD-L1 interaction in this case is apoptosis of the activated tumor-specific T cells and hence, immune escape. In HL, neoplastic HRS cells are surrounded by an extensive but ineffective inflammatory tumor microenvironment. Chromosome 9p24.1 amplification is frequently present...
in HRS cells, resulting in PD-L1 and PD-L1 overexpression.

Nivolumab (BMS-936558) is a fully human monoclonal IgG4 antibody against PD-1. The results of a phase I dose expansion cohort study of nivolumab in 23 heavily pretreated patients with relapsed/refractory HL showed an impressive ORR of 87% (17% CR, 70% partial response), and 13% of patients had SD.73 Response occurred within the first 8 weeks of therapy in 60% of all responders. PFS at 24 weeks was 86% with a median follow-up of 40 weeks. Patients were treated with 3 mg/kg at week 1, week 4, and then every 2 weeks until disease progression, CR, or intolerable toxicity, for a maximum of 2 years. A total of 78% of patients had been treated with BV and 78% had an auto-SCT before enrollment. No drug-related grade 4 adverse events occurred, whereas drug-related grade 3 adverse events occurred in 22% of patients, mostly in the form of autoimmune reactions, such as hypothyroidism (2 patients) and pancreatitis (1 patient), pneumonitis (1 patient), and colitis (1 patient). Rash (22%) and thrombocytopenia (17%) were the most common drug-related adverse events overall. The drug was discontinued in 52% of patients (9% with toxic effects, 17% with disease progression, and 26% for initiation of alternative therapies). In all 10 patients with evaluable samples, HRS expressed PD-L1 and PD-L2 proteins and had amplification of the corresponding genetic loci. The results of this study in heavily pretreated patients with otherwise limited expected survival led the FDA to grant nivolumab breakthrough therapy designation for patients with HL after failure of auto-SCT and BV. The international phase II registration study is nearly complete.

Pembrolizumab (MK-3475) is also a humanized monoclonal IgG4 antibody against PD-1, which is FDA-approved for metastatic melanoma. It is being evaluated in patients with relapsed/refractory HL who received prior treatment with BV in the phase Ib KEYNOTE-013 trial (ClinicalTrials.gov identifier: NCT01953692). Treatment consists of pembrolizumab given at 10 mg/kg every 2 weeks. Discontinuation is allowed for those with CR; in the remaining patients, the drug is continued for up to 2 years or until disease progression or intolerable toxicity. Preliminary results reported that, at a median follow-up of 153 days, 70% of patients remained on therapy, whereas 30% had discontinued treatment (3% because of CR, 24% because of progressive disease, and 3% from adverse events).74 Hypothyroidism and pneumonitis were the most common adverse events, each occurring in 10% of patients. No grade 4 adverse events occurred, and only one grade 1 adverse event (autoimmune colitis) occurred. The ORR was 66% (CR, 21%), and disease remained stable in 21%. The median time to response was 12 weeks, and the median duration of response had not been reached. All 10 patients with an evaluable sample showed PD-L1 expression.

Conclusions

Similar to solid tumors and other hematologic malignancies, the treatment of HL has been heavily influenced by biologic therapies. Although the history of biologic therapies in HL dates back several decades, only recently have such approaches emerged as promising additions and potential alternatives to aggressive multiagent chemotherapy or radiation. Considering the adverse long-term consequences of cytotoxic chemotherapy and radiation, biologic therapies may become an essential component of treatment in HL. Currently, the approved use of biologic agents in HL is limited to the relapsed/refractory setting, but interesting data are also accumulating from clinical trials in the frontline setting. To date, BV has been the most successful biologic agent in HL, with high response rates and durable remissions in a small subset of patients with multiply relapsed or refractory disease. Checkpoint inhibitors (nivolumab and pembrolizumab) seem to be another promising approach. These agents offer the opportunity to address conventional and high-dose chemotherapy resistance, either in the relapsed or frontline setting. Although the standard treatment for HL has remained largely consistent for the past several decades, it may undergo fundamental changes in the near future with the addition of effective biologic therapies.

References


