



# Therapies for Relapsed Hodgkin Lymphoma: Transplant and Non-Transplant Approaches Including Immunotherapy

Nancy L. Bartlett

**Autologous stem cell transplant remains the standard of care for relapsed Hodgkin lymphoma (HL). Approximately 50% of patients with chemo-sensitive relapse will be cured with this approach. The optimal pretransplant salvage regimen is controversial, but less toxic combinations seem to be equivalent to more aggressive approaches. For patients with chemo-refractory disease at relapse and those failing autolo-**

**gous transplant, the long-term prognosis remains poor. New approaches such as reduced-intensity allogeneic transplant, monoclonal antibodies targeting the CD30 antigen, Epstein-Barr virus (EBV)-specific cytotoxic T-lymphocytes, and bortezomib are under investigation, but preliminary results are disappointing. New therapies are needed for patients with relapsed HL.**

During the last decade, the questions regarding the treatment of relapsed Hodgkin lymphoma (HL) have changed. There is no longer a need to address treatment of relapse after primary radiotherapy, as this approach to HL has virtually disappeared. In addition, controversy surrounding the optimal timing (first vs second relapse) of autologous stem cell transplantation (auto-SCT) after failure of primary chemotherapy (CT) has largely subsided. Results of a large randomized trial from the German Hodgkin Study Group (GHSG) and European Group for Blood and Marrow Transplantation (EBMT) published in 2002 and updated at the American Society of Clinical Oncology (ASCO) 2005 meeting showed freedom from treatment failure was significantly better for patients undergoing transplant compared to non-transplant salvage, regardless of whether they relapsed early (< 12 months) or late following primary chemotherapy.<sup>1,2</sup>

Novel approaches to the primary treatment of HL and additional options for the treatment of relapsed disease have resulted in new questions.

- Should patients who receive chemotherapy alone for early stage disease and have a localized relapse at the site(s) of initial disease receive radiotherapy (RT) or high-dose therapy and transplant at the time of first relapse?
- What options are available for patients relapsing after aggressive first-line regimens such as dose-escalated BEACOPP?
- Given the marked decrease in mortality following allogeneic transplant with reduced intensity conditioning (RIC), are there circumstances where this approach would be favored over autologous stem cell transplantation?
- How should newer agents with activity in HL, such as vinorelbine and gemcitabine, be incorporated into treatment of relapsed disease?

Unfortunately, studies are not yet available to answer these questions completely. This review will summarize the recent literature regarding treatment of relapsed HL including prognostic factors, pre-transplant salvage regimens, advances and long-term follow-up of auto-SCT, use of RIC with allogeneic transplant (RIC-allo), and the continued search for new drugs including an active monoclonal antibody for HL.

## Prognostic Factors

Many prognostic factors have been described for patients relapsing after first-line chemotherapy including stage, time to relapse, B symptoms, extranodal disease, performance status, anemia, and gender. Inconsistent findings among studies are attributable to small patient numbers, inclusion of patients with primary refractory disease, and in some series lack of multivariate analysis. Now that most patients less than about age 70 with relapsed disease would be considered appropriate candidates for auto-SCT, these models are less likely to have an impact on choice of initial therapy for relapsed disease. However, a reproducible prognostic model would provide a more accurate assessment of outcome for patients, allow comparison across trials based on patient characteristics, and perhaps identify a small set of patients with such a dismal outcome that new approaches would be chosen over standard auto-SCT.

In the largest series to date, Josting et al from the GHSG developed a prognostic score for relapsed HL based on outcomes of 471 patients who failed primary therapy.<sup>3</sup> In multivariate analysis, independent risk factors were time

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Correspondence: Nancy L. Bartlett, MD, Washington University School of Medicine, Siteman Cancer Center, 660 S. Euclid, Box 8056, St. Louis, MO 63110; Phone (314) 362-5652, Fax (314) 362-7086, nbartlet@im.wustl.edu

to relapse ( $\leq 12$  mo vs  $>12$  mo), clinical stage at relapse (stage III or IV), and anemia at relapse (males  $<12$  g/dL; females  $<10.5$  g/dL). Five-year freedom from second failure (FF2F) rates for patients failing primary chemotherapy or combined modality therapy were approximately 45%, 32%, and 18% for patients with prognostic scores of 0-1, 2, and 3, respectively. Only 8% of patients had all 3 poor prognostic factors, with 70% having a score of 0-1. Bierman et al evaluated the International Prognostic Factors Project Score (IPS) developed for newly diagnosed advanced stage HL in 379 patients who underwent auto-SCT for relapsed HL.<sup>4</sup> In multivariate analysis, of the seven prognostic factors in the IPS, low serum albumin, anemia, age, and lymphopenia were associated with inferior event-free survival (EFS) and overall survival (OS). Gender, stage and leukocytosis were not significant. Estimated 10-year EFS rates were 38%, 23%, and 7% for patients with 0-1 ( $n = 27\%$ ), 2-3 ( $n = 53\%$ ) or  $\geq 4$  ( $n = 20\%$ ) of the seven IPS risk factors. While both of these recent models clearly define prognostic groups, outcomes for even the best patients in these models are disappointing and underscore the need for better therapies for relapsed HL. In addition, models based on characteristics at relapse do not take into account response to second-line therapy, an important prognostic factor in most auto-SCT series.

### Pretransplant Salvage Regimens

There continues to be no clear “winner” among pretransplant salvage regimens for relapsed HL. No randomized trial exists comparing the effectiveness of conventional salvage regimens. Historically, there have been two primary approaches. Many European centers have favored aggressive pretransplant regimens such as mini-BEAM and DEXA-BEAM.<sup>1,2,5</sup> These intensive regimens are associated with significant hematologic toxicity and a 2%-5% treatment-related death rate, similar to rates seen with auto-SCT. Most other centers have utilized platinum-based regimens such as ICE, DHAP, ESHAP, or ASHAP in an effort to introduce non-crossresistant drugs.<sup>6-9</sup> Due to reports of high single-agent activity in relapsed HL, a few new salvage regimens have incorporated gemcitabine.<sup>10-14</sup>

Overall and complete response (CR) rates for selected pretransplant salvage regimens are listed in **Table 1**. Comparison of OS and EFS rates is difficult. Some series, such as the large randomized trial of DEXA-BEAM  $\pm$  auto-SCT report follow-up only for patients who responded to DEXA-BEAM.<sup>1</sup> Other reports include follow-up on all patients participating in the conventional salvage protocol, regardless of additional therapy. Three-year EFS rates range from 27% for ESHAP, where only 9 of 22 patients went on to transplant, to

58% for ICE, where 56 of 65 patients went on to transplant.

Now that randomized trials have shown a benefit to auto-SCT for relapsed HL, the choice of a pretransplant salvage regimen should be based on the potential to induce high-response rates with low toxicities, allowing the majority of patients to proceed without delay to high-dose therapy. The recently reported gemcitabine-based regimens seem particularly appealing due to low reported rates of grade 3-4 toxicity and response rates in the range of those seen with more toxic regimens.<sup>12-14</sup> Investigators for the National Cancer Institute of Canada reported on 23 patients with relapsed HL treated with gemcitabine 1000 mg/m<sup>2</sup> days 1 and 8, cisplatin 75 mg/m<sup>2</sup> on day 1 and dexamethasone 40 mg/d on days 1-4 every 21 days.<sup>12</sup> Overall response rate was 70% with no grade 4 neutropenia or thrombocytopenia, 8% grade 3 neutropenia, and 13% grade 3 thrombocytopenia. All patients had successful stem cell collection and underwent auto-SCT. CALGB investigators reported preliminary results of a salvage regimen for relapsed HL including gemcitabine 1000 mg/m<sup>2</sup> on days 1 and 8, vinorelbine 20 mg/m<sup>2</sup> on days 1 and 8, and liposomal doxorubicin 15 mg/m<sup>2</sup> on days 1 and 8 every 21 days.<sup>14</sup> Updated results for the 50 patients who had not undergone a prior SCT show an overall response rate of 60%, no toxic deaths and a 7% incidence of fever and neutropenia without the use of growth factors (manuscript in preparation). The 3-year EFS and OS rates were 60% and 80%, respectively. These numbers compare favorably to the 3-year EFS and OS rates of 58% and 73% reported by Moskowitz et al for the comprehensive 2-step program of ICE + auto-SCT.<sup>6</sup>

### Autologous Stem Cell Transplantation

The use of auto-SCT for relapsed HL is now considered the standard of care. Two randomized trials showed significant benefit in freedom from treatment failure (FFTF) for auto-SCT over conventional therapy for relapsed disease.<sup>1,2,15</sup>

**Table 1. Comparison of selected standard pre-transplant salvage regimens for Hodgkin's lymphoma.**

Regimen	Ref.	# of Pts.	RR (CR)	Toxic Deaths
Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan)	1	144	81% (27%)	5%
Mini-BEAM (carmustine, etoposide, cytarabine, melphalan)	5	55	82% (49%)	2%
ICE (ifosfamide, carboplatin, etoposide)	6	65	88% (26%)	0%
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)	8	22	73% (41%)	5%
ASHAP (doxorubicin, methylprednisolone, cytarabine, cisplatin)	9	56	70% (34%)	0%
GVD (gemcitabine, vinorelbine, liposomal doxorubicin)	14	50	60% (20%)	0%
GDP (gemcitabine, dexamethasone, cisplatin)	12	23	69% (17%)	0%

Abbreviations: RR, response ratio; CR, complete response.

The results of these trials, together with improved tolerability of the procedure, have resulted in the recommendation of auto-SCT at time of first relapse for even the most favorable patients. The lack of a survival benefit in these randomized trials has been attributed to patients in the non-transplant arm undergoing transplant at the time of second relapse.

### **Randomized trials**

Investigators for the GHSG and EBMT reported on 161 patients with relapsed HL randomized to standard dose Dexamethasone-BEAM or high-dose BEAM and transplantation with hematopoietic stem cells (BEAM-HSCT).<sup>1</sup> Of the 117 patients with chemosensitive relapse there was a significant improvement in 3-year FTF for patients undergoing auto-SCT compared to 4 cycles of Dexamethasone-BEAM (55% vs 34%,  $P = 0.019$ ). Three-year FTF was significantly better for patients treated with BEAM-HSCT, regardless of whether first relapse occurred *early* (< 12 months) (41% vs 12%  $P = 0.007$ ) or *late* (>12 months) (75% vs 44%,  $P = 0.02$ ). There was no statistically significant difference in OS for any subgroup. Schmitz and colleagues presented an update of their data at ASCO 2005 with 7-year FTF rates continuing to show an advantage for BEAM-HSCT (49% vs 32%,  $P = 0.02$ ) but no difference in 7-year OS rates.<sup>2</sup> There was no difference in 7-year FTF for patients with "multiple relapses" prior to trial entry (32% for Dexamethasone-BEAM vs. 27% for BEAM-HSCT), however the number of such patients on the trial was small ( $n = 24$ ).

The only other randomized trial of transplant for relapsed disease was a small trial from the British National Lymphoma Investigation (BNLI) comparing auto-SCT with BEAM as a preparative regimen to mini-BEAM without auto-SCT.<sup>15</sup> Only 20 patients were accrued to each arm.<sup>15</sup> Despite the small numbers, there was a significantly improved 3-year EFS in patients undergoing auto-SCT compared to mini-BEAM (53% vs 10%,  $P = 0.025$ ) with no difference in OS. Interestingly, in contrast to the GHSG trial, all but 2 patients in both arms had either never achieved a complete response or had refractory or untested relapse. Despite this, the 3-year EFS rate of 53% in the auto-SCT group was nearly identical to the 55% reported in the GHSG transplant arm for patients with chemosensitive relapse.

The lack of survival difference in these two trials suggests that auto-SCT at first or second relapse provides comparable outcomes. Avoiding the short- and long-term toxicities of multiple salvage regimens and the potential anxiety associated with multiple relapses, in combination with the acceptable mortality and morbidity rates associated with auto-SCT, compels most physicians to recommend auto-SCT at first relapse.

### **Primary refractory disease**

As opposed to non-Hodgkin lymphoma (NHL), where chemo-refractory patients are not salvaged by transplant,

there seems to be a general consensus that even patients who fail first- and second-line chemotherapy may still enjoy a 20%-30% chance of cure with auto-SCT. However, as highlighted by Josting et al, reports of auto-SCT for primary-refractory disease are subject to significant selection bias.<sup>16</sup> Patients with rapidly progressive disease, poor performance status, older age and poor stem cell harvest are not included in the reports. The GHSG, in a landmark analysis comparing patients with primary refractory disease who did or did not receive transplant within 6 months of progression, and excluding all patients who survived less than 6 months, showed no advantage to auto-SCT.<sup>16</sup>

A report from Memorial Sloan Kettering Cancer Center summarized the long-term outcome of 75 consecutive patients with biopsy-confirmed HL at the completion of primary chemotherapy or combined modality therapy.<sup>17</sup> All patients underwent standard-dose salvage therapy followed by involved field radiotherapy (IFRT) to sites of active disease. Patients without progression went on to receive high-dose etoposide, cyclophosphamide and either total lymphoid irradiation (if no prior RT) or carmustine (if prior RT) followed by bone marrow or peripheral stem cell rescue. Seven patients were excluded from transplant because of progression on standard salvage therapy and had a 4 month median survival. Patients with less than a 25% decrease with standard salvage therapy ( $n = 27$ ) had a 10-year EFS of 17% versus 60% for those with at least a 25% decrease to standard second-line therapy ( $n = 48$ ).

Ferme et al from the GELA reported on 157 patients with either induction failure (IF), partial response of less than 75%, or relapse after doxorubicin-based chemotherapy  $\pm$  RT.<sup>18</sup> All patients received mitoguanine, ifosfamide, vinorelbine, and etoposide (MINE) as second-line therapy followed by auto-SCT with BEAM as the preparative regimen. The 5-year OS rates were 30% for patients with IF versus 72% for patients with < 75% partial response (PR) and 76% for patients with relapsed disease following first-line therapy. Of the 101 patients who went on to transplant, the 5-year FF2F rate for patients with a response to MINE was 64% versus 25% for those not responding to MINE. Of the 64 patients with IF, 40 responded to second- or third-line salvage therapy and 32 of these patients went on to transplant. Of the 24 patients not responding to salvage, 9 went on to transplant, only 1 of whom achieved a CR with auto-SCT.

In conclusion, most large transplant series continue to show that response to conventional chemotherapy pretransplant is highly predictive of outcome. Patients with primary refractory disease who respond to a second-line salvage regimen still have a reasonable outcome with auto-SCT. Those with no response to first- or second-line therapy are candidates for new approaches as described below. Reports of a 15% 5- or 10-year survival in completely refractory patients undergoing auto-SCT may justify this approach in an otherwise healthy young patient without other options.

### Preparative regimen

As with the pretransplant salvage regimens, there has never been a randomized trial comparing preparative regimens for transplant for relapsed HL. The only recent article to address this question was a retrospective review by investigators at the Fred Hutchinson Cancer Research Center. Between 1990 and 1998, 92 patients with relapsed HL were transplanted with either a total body irradiation (TBI)-based regimen (TBI/cyclophosphamide/etoposide) or busulfan/melphalan/thiotepa.<sup>19</sup> The choice of preparative regimen was based primarily on whether or not the patient had a prior history of dose-limiting radiation. There was no difference in 5-year OS (57% vs 52%) or EFS (49% vs 42%) rates for patients treated with TBI or chemotherapy only. Older retrospective comparisons reported similar results. Given the reports of increased risk of second cancers and myelodysplasia following TBI, a chemotherapy only preparative regimen is currently favored by most transplant centers.<sup>20</sup>

### Prognosis post-failed auto-SCT

The median survival for patients with relapse post-transplant is approximately 2 years, with the most important predictor of outcome being response to salvage therapy.<sup>21,22</sup> The GELTAMO recently reported on 175 patients who relapsed after auto-SCT with 3-year OS and progression-free survival (PFS) of 35% and 23%, respectively.<sup>23</sup> In multivariate analysis, an interval of < 12 months since auto-SCT and stage III-IV disease at relapse were predictors of poor outcome. Patients with both features had 3-year PFS of 14% compared to 48% for patients without either factor.

### Second auto-SCT

All data regarding second auto-SCT for relapsed HL are anecdotal, with most series reporting results of  $\leq 5$  patients. The most favorable results are for those patients who achieve a CR with their first transplant and have a prolonged remission post-transplant.<sup>24,25</sup> In most series, early and late treatment-related mortality (TRM) is high, with most deaths related to infection or interstitial pneumonitis.

### Allogeneic Stem Cell Transplantation

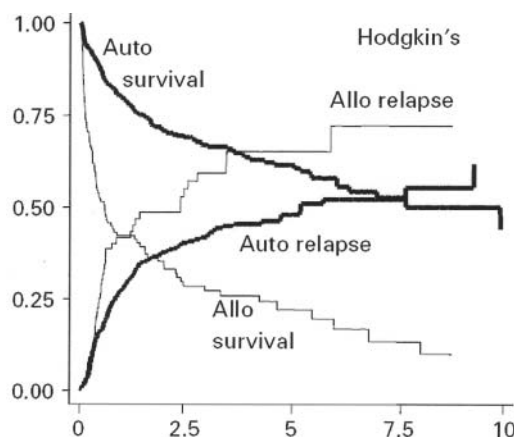
High TRM and poor outcomes with conventional allo-SCT as either first or second transplant have dampened enthusiasm for this approach.<sup>26-28</sup> An EBMT registry-matched study of conventional allo-SCT versus auto-SCT as first transplant reported a 4-year OS rate of 24% for allo compared to approximately 60% for auto (**Figure 1**).<sup>26</sup> Akpek et al from Johns Hopkins reported no difference in relapse rates, EFS or OS for 53 patients undergoing allo-SCT compared to 104 patients having auto-SCT for relapsed HL.<sup>27</sup> A recent review of IBMTR/ABMTR data identified 114 patients (79 NHL, 35 HD) who underwent a conventional allo-SCT (1990–1999) after failing an auto-SCT.<sup>28</sup> The PFS rates at 1, 3, and 5 years of 32%, 25%, and 5%, respectively, with no difference in HL and NHL, and TRM was 21% at 100 days.

### Reduced intensity conditioning allogeneic transplant

The recent emphasis on reduced intensity conditioning with allogeneic transplant (RIC-allo) has renewed interest in the use of allo-SCT for relapsed/refractory HL. Because only minimal or modest tumor suppression is expected from the conditioning, any chance of cure with this approach is expected to come from graft-versus-tumor effect. Therefore, this approach is probably not indicated for patients where immediate disease control is essential. Outcomes data for RIC-allo is limited, with most of the data for HL in the setting of failed auto-SCT. Between 1996 and 2001, data on 181 conventional allo-SCT and only 33 RIC-allo for HL were reported to the IBMTR.<sup>29</sup>

In 2002, Kogel and McSweeney identified 75 patients in the literature who had undergone RIC-allo for HL.<sup>29</sup> Of the 75 patients, 49% achieved CR or were reported as “alive and well,” 9.3% had a PR, 20% died of progressive disease and remarkably there were only 5.3% non-relapse related deaths. No information is provided about the disease status at time of transplant or remission duration. The EBMT collected data on 94 patients who received RIC-allo for HL.<sup>30</sup> Nearly 50% had failed previous autograft. Three-year OS, PFS, and TRM rates were 45%, 35%, and 18%, respectively. The only significant prognostic factor for OS and disease-free survival was chemosensitive disease, with a median survival of less than a year for patients with resistant disease, while the median had not yet been reached at 2 years in patients with sensitive relapse.

Several small, preliminary single institution or consortium series have also been reported in the last few years. Unfortunately, many of these series report HL and NHL patients together. Faulkner et al reported on 65 patients (only 5 with HL) undergoing RIC-allo with BEAM plus Campath as conditioning.<sup>31</sup> TRM was only 7% for those undergoing first transplant versus 57% for those previously treated with auto-SCT. OS was 80% at 1 year. Branson et al



**Figure 1.** Overall survival and relapse rate for autologous versus allogeneic transplant in a matched analysis of EBMT registry.<sup>26</sup>

reported a 14-month OS of 83% and TRM of 20% in 12 patients with HL who received RIC-*allo*.<sup>32</sup> With a median follow-up of 14 months, 5 remain in CR and 4 have “non-progressive disease.” Anderlini et al from MD Anderson reported 18-month OS and PFS rates of 73% and 46% for 26 patients with relapsed HL undergoing RIC-*allo* with fludarabine and melphalan as conditioning.<sup>33</sup> Three-quarters had failed prior auto-SCT and 100-day TRM was 5%. In another series of 40 patients with recurrent HL undergoing RIC-*allo* as either a first (11) or second (29) transplant 2-year OS and EFS were 48% and 20%, respectively.<sup>34</sup> Resistant disease was the only predictor of poor outcome. Interestingly, 11 patients received donor lymphocyte infusions (DLI) for PD with 3 patients achieving CR and 3 PR.

Carella et al piloted tandem transplants in 10 patients with “high-risk” relapsed HL. All patients underwent an auto-SCT with BEAM conditioning followed by RIC-*allo*, a median of 61 days after engraftment.<sup>35</sup> Four of the 10 patients had primary refractory HL, 1 was in first PR and 5 were in relapse, 1-4 having achieved previous CR to therapy. One patient in CR died from brain aspergillus, 2 died of progressive disease (PD), 2 are alive with relapse, and 5 remain in remission a median of 335 days post RIC-*allo*. While an interesting approach, there are too few patients to draw any conclusions and it is unclear that the eligibility criteria defined a group with poor outcome with auto-SCT alone.

### **Graft-versus-lymphoma**

The high relapse rates reported in most early series of *allo*-SCT raised uncertainty about a significant graft-versus-lymphoma (GVL) effect in HL. However, the increased TRM rates and inclusion of primarily patients with refractory disease may have obscured a beneficial effect in initial reports.<sup>36</sup> When allogeneic transplant was done early in the course of disease, Akpek et al showed a lower relapse rate compared to auto-SCT, suggesting a GVL effect.<sup>27</sup> Reports of responses to DLI following disease relapse or progression, and decreased relapse rates in patients with either acute or chronic GVHD also substantiate a GVL effect in HL.<sup>34,36,37</sup>

### **Radiotherapy**

Historical data confirm that there are occasional patients where RT alone for a limited relapse results in a long-term remission. Because previous series were small and subject to selection bias, the overall benefit and applicability of this approach are hard to define. In 2005, Josting et al reported the most comprehensive series of salvage radiotherapy alone in 100 patients with primary progressive or relapsed HL.<sup>38</sup> With a median observation time of 52 months, 5-year FF2F and OS for all patients were 28% and 51%, respectively, and for patients with limited stage at progression/relapse, 22% and 55%, respectively.

## **New Agents**

### **Monoclonal antibodies**

The search for effective monoclonal antibodies for HL has been disappointing. Recent efforts have focused on the CD30 antigen, an attractive target as it is expressed in nearly all cases of classical HL and expression on normal tissue is highly restricted. Despite encouraging preclinical studies, clinical activity of these antibodies has been limited. In a phase II study of the chimeric anti-CD30 antibody SGN-30, there were no objective responses in 21 patients.<sup>39</sup> Results were slightly more promising with the humanized anti-CD30 antibody, MDX-060, with 4 of 40 patients responding.<sup>40</sup> Because preclinical studies have shown potential synergy between anti-CD30 antibodies and several chemotherapy agents with activity in HL including doxorubicin, bleomycin, vinblastine, dacarbazine, and gemcitabine, clinical trials are underway to test combination therapy.

Other approaches to harnessing the benefits of targeted therapy include immunoconjugates and radiolabeled antibodies. Preclinical studies of cAC10-vcMMAE, an immunoconjugate of the SGN-30 antibody and monomethyl auristatin E (MMAE), a synthetic analog of the tubulin inhibitor dolastatin 10, has shown significant activity against HL in SCID mice.<sup>41</sup> There was no toxicity at doses of MMAE that were 100 times the maximum tolerated dose (MTD) of free MMAE. Clinical trials with this agent are in development. Schnell et al reported a 29% response rate to an <sup>131</sup>I-anti-CD30 radiolabeled antibody in 21 patients with relapsed HL, including 19 who failed prior auto-SCT.<sup>42</sup>

There has been some interest in the use of the anti-CD20 antibody rituximab in patients with relapsed classical HL. Most series show 10%-20% of classical HL express at least low levels of CD20 antigen. Younes et al from MD Anderson Cancer Center reported a response rate of 22% in 22 patients with relapsed HL, with median remission duration of 7.8 months. B symptoms were relieved in 6 of 7 patients.<sup>43</sup> Only 6 of the 22 patients were CD20<sup>+</sup> and responses were independent of CD20 status. The authors hypothesize the clinical benefit may be attributable to the elimination of benign B-cells which support the Reed-Sternberg (RS) cells. Further studies are needed before this is routinely incorporated into the treatment of patients with relapsed HL.

### **EBV-specific cytotoxic T-lymphocyte therapy**

Epstein-Barr virus (EBV) proteins are present in RS cells in about 40% of patients with HL, representing a potential target for immunotherapy. While the use of immunotherapy with cytotoxic T-lymphocytes (CTLs) has shown significant promise in EBV-associated lymphoproliferative disorders occurring after *allo*-SCT and solid organ transplant (PTLD), this approach has had limited success in EBV<sup>+</sup> HL.<sup>44</sup> In contrast to PTLT, the RS cells have developed mechanisms to evade virus-specific CTL including downregulation of the immunodominant EBV antigens and secretion of cytokines such as tumor necrosis factor (TNF) $\beta$

that inhibit CTL. Despite these obstacles, responses have been reported with this approach. Of 14 patients treated with EBV-specific CTLs, 5 patients were in CR up to 40 months after treatment, 2 of whom had measurable disease at the time of treatment.<sup>44</sup> One additional patient had a PR. In addition to infusing EBV-specific CTL lines as described above, preclinical studies have shown hopeful results with both a latent membrane protein (LMP1) polypeptide vaccine which generated strong LMP1-specific CTL responses and reversed tumor growth of LMP1-expressing tumors, and dendritic cells transduced with a recombinant adenoviral vector expressing inactive LMP1.<sup>45,46</sup>

### Chemotherapy agents

The search continues for new chemotherapy agents for relapsed HL. As described earlier, efforts to incorporate gemcitabine into both first-line and salvage therapies for HL are underway.<sup>10-14</sup> A phase II study of liposomal vincristine showed a 29% response rate in 21 evaluable patients.<sup>47</sup> The proteasome inhibitor bortezomib has shown very limited activity in heavily pretreated HL, with 1 of 8 patients having a PR in one series.<sup>48</sup> Preliminary results of a phase II CALGB study of bortezomib for HL are also discouraging, but formal analysis is still underway.

### Conclusions

Patients with relapsed HL have a chance of cure. The most favorable results are for those patients with a more durable first remission and those responding to conventional salvage therapy. In these subsets, approximately 50% will be cured with auto-SCT. Despite this relatively favorable prognosis for chemosensitive patients, further attempts to improve the outcome of these patients is warranted. The current GHSG trial is comparing a conventional BEAM-HSCT to sequential high-dose therapy followed by BEAM for these patients.<sup>49</sup> New approaches are needed for chemoresistant HL, where there is less than a 20% chance of long-term remission with autologous or allogeneic SCT. The data for RIC-allo are preliminary and many questions remain, including the choice of RIC regimen, the role of RIC-allo as first versus second transplant, and most importantly proof of a GVL effect in HL, the premise of considering this approach in any hematologic malignancy. Monoclonal antibody development has not been successful so far, but immunoconjugates may represent a more effective targeted therapy.

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