

Salvage Regimens for Hodgkin Lymphoma

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Abstract: There are many effective salvage chemotherapy regimens for the treatment of patients with Hodgkin lymphoma (HL) who relapse after or are refractory to primary therapy. All eligible patients with relapsed or refractory HL should be considered for high-dose chemotherapy with autologous stem cell transplantation. This type of therapy has become the standard of care for patients with chemosensitive disease, based on numerous phase II and two phase III clinical trials. The major considerations in the choice of salvage therapy are response rate, toxicity, and effect on subsequent stem cell collection. For patients who do not respond to salvage therapy or who relapse after autologous transplantation, available treatment options include additional salvage regimens, reduced-intensity allogeneic stem cell transplantation, and investigational agents. This review summarizes the results of various salvage chemotherapy regimens, including newer regimens that incorporate gemcitabine, in addition to novel therapies that are currently being studied in patients with relapsed or refractory HL.

The majority of patients with Hodgkin lymphoma (HL) are cured with first-line multiagent chemotherapy, often in combination with radiotherapy for early stage disease. ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is the most commonly used initial therapy for HL due to its high response rate and relatively low toxicity.¹ The more intensive escalated BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) is associated with a higher response rate and better disease-free survival but is more toxic.² Despite the availability of these highly effective regimens, 15–20% of patients with early stage HL and 35–40% of those with advanced stage HL will progress or relapse after initial therapy.^{3,4} These patients will require salvage therapy, and most will proceed to autologous stem cell transplantation (ASCT).

A number of prognostic factors have been identified for relapsed HL, including time to relapse (≤ 12 or > 12 months), clinical stage at relapse, anemia, prior therapy, and older age.⁵⁻⁸ However, the most consistent predictors of outcome are the response to salvage therapy and the presence of detectable disease at the time of trans-

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plantation.⁹⁻¹¹ For instance, in an analysis of data from the Spanish Cooperative Group registry, 5-year time to treatment failure for patients with second complete remission (CR), chemosensitive disease, and chemoresistant disease at the time of transplant was 68%, 34%, and 11%, respectively.⁸ Functional imaging with ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans provides a sensitive assessment of residual lymphoma; a negative PET scan prior to transplantation has been associated with a significant decrease in the risk of relapse.^{12,13} In one report, the relapse rate was 72% for HL patients with a positive PET scan prior to ASCT, but only 23% for those with a negative PET scan.¹⁴ Larger studies are needed to determine the role of PET scans in clinical decision making during salvage therapy, but the prognostic importance of the response to salvage therapy is unquestionable.

Because no randomized trials comparing salvage chemotherapy regimens have been performed, the choice of therapy for relapsed HL must be based on data from single-arm studies and retrospective analyses. Given that disease status at the time of transplant is a major determinant of long-term outcome, the optimal salvage regimen will have a high response rate with manageable toxicity. Also, the effect of the salvage regimen on stem cell collection must be considered for patients who will be proceeding to ASCT.

Autologous Stem Cell Transplantation

A number of single-arm studies and two randomized trials have established ASCT as the standard of care for chemosensitive, relapsed HL. Phase II and retrospective studies of ASCT, which include a mixture of primary refractory and multiply relapsed patients, report 4–5 year progression-free survival (PFS) and overall survival (OS) rates of 25–50% and 45–58%, respectively.¹⁵⁻¹⁹ Two relatively small, randomized trials established the superiority of ASCT over standard-dose chemotherapy. A trial conducted by the British National Lymphoma Investigation (BNLI) randomly assigned 40 patients with high-risk relapsed or refractory HL to conventional chemotherapy with mini-BEAM (carmustine, etoposide, cytarabine, and melphalan) or BEAM and ASCT.²⁰ The event-free survival (EFS) was statistically better in the ASCT arm (53% vs 10%) compared to the mini-BEAM arm, but there was no difference in OS between the 2 groups. The German Hodgkin Study Group and the European Group for Blood and Marrow Transplantation (GHSG/EBMT) conducted a larger randomized trial comparing salvage chemotherapy alone to salvage chemotherapy followed by high-dose chemotherapy and ASCT.^{21,22} One hundred sixty-one patients with relapsed

HL were treated with two cycles of DEXA-BEAM (dexamethasone, BEAM), and the 117 patients who had a CR or partial response (PR) were randomly assigned to two additional cycles of DEXA-BEAM or BEAM/ASCT. Seven-year freedom from treatment failure (FFTF) favored the BEAM/ASCT arm (49% vs 32%; $P=.02$), but, as in the BNLI trial, there was no statistically significant difference in OS between the two treatment arms. The failure to find an improvement in OS with ASCT has been attributed to the fact that many patients treated with chemotherapy alone underwent ASCT at second relapse. Because ASCT clearly improved PFS, these studies established ASCT as the standard of care for patients with a first relapse of HL.

Given the prognostic significance of response prior to transplant, the question arises whether patients with chemoresistant disease should undergo ASCT. Retrospective studies demonstrate that even patients with primary refractory disease can benefit from ASCT, with 5-year FFTF ranging from 15% to 39%.²³⁻²⁵ However, chemosensitivity prior to transplant remains an important prognostic factor: patients who fail to respond to both initial and salvage therapy have a PFS of less than 20% after ASCT.^{26,27} Consequently, patients who progress on salvage therapy should be treated with additional lines of non-crossresistant chemotherapy or with investigational approaches. The appropriate treatment for patients who have stable disease or minimal response after salvage therapy is less clear. Our practice is to treat these patients with additional lines of therapy to optimize their response before proceeding to transplant. Autologous or allogeneic stem cell transplantation (SCT) can be considered if patients subsequently achieve significant reduction in their disease burden.

Salvage Chemotherapy Regimens

Patients with relapsed HL who proceed to ASCT benefit from a salvage chemotherapy regimen that provides a high response rate, low toxicity, and minimal detriment to subsequent autologous stem cell collection. Patients who relapse after a first CR lasting more than 12 months have a response rate of 50–80% to salvage therapy, whether treated again with the initial regimen or with a new regimen.^{28,29} However, the current widespread use of the anthracycline-containing regimen ABVD in frontline treatment limits the reintroduction of initial therapy for most patients. Also, patients who relapse in less than a year, or who have primary refractory disease, have demonstrated resistance to the initial regimen. For these reasons, salvage regimens containing non-crossresistant agents will be required for the majority of patients.

Dexa-BEAM and Mini-BEAM

Dexa-BEAM and mini-BEAM incorporate the drugs commonly used in transplant conditioning regimens. These regimens are relatively intensive and are associated with prolonged cytopenias and treatment-related mortality of 2–5%. In addition, they contain stem cell–toxic agents that may make stem cell collection difficult.^{30,31} In the GHSG/EBMT trial, there was no difference in the frequency of grade 3/4 toxicities between patients treated with Dexa-BEAM and those who underwent ASCT. In that study, the overall response rate (ORR) to two cycles of Dexa-BEAM was 81% (CR 27%), and responding patients who did not proceed to ASCT had 3-year FFTR and OS of 34% and 65%, respectively.

Martin and colleagues evaluated 55 patients with relapsed or refractory HL who were treated with 2–4 cycles of mini-BEAM.¹¹ The ORR was 84% (CR 51%) and all responding patients underwent ASCT. Toxicities included 1 death, grade 4 neutropenia in 86% of patients, and hospitalization due to fever in 61% of patients. Also, there was a 5.4% incidence of secondary neoplasias. Only 20 of 36 patients (56%) who underwent mobilization of peripheral blood stem cells (PBSC) achieved a collection of more than 2×10^6 CD34+ cells/kg. At a median follow-up of 68 months, 7-year EFS was 36%, a result similar to other transplant series using less toxic salvage regimens. The morbidity, mortality, and stem cell toxicity of this regimen compared to other salvage regimens make it a less appealing pretransplant option.

Platinum-based Regimens

The commonly used platinum-based salvage regimens have a more tolerable toxicity profile than Dexa-BEAM and mini-BEAM, with similar response rates. However, PFS attributable to these regimens is difficult to assess, as most of the responding patients in the reported trials proceeded to ASCT.

The combination of etoposide, methylprednisolone, high-dose cytarabine, and cisplatin (ESHAP) had an ORR of 73% in one small study, with grade 3/4 myelotoxicity occurring in 59% of patients.³² A larger, multi-institutional study reported the outcome of patients with relapsed or refractory HL treated with ESHAP (n=78) or DHAP (cisplatin, cytarabine, dexamethasone; n=27).³³ The ORR was 78% (CR=39%), and grade 4 neutropenia or thrombocytopenia occurred in 26% and 7% of cycles, respectively. Two patients died of procedure-related complications. PBSCs were collected after the second or third cycle of therapy, and 97% of patients met the minimum collection of over 2×10^6 CD34+ cells/kg.

In a multicenter German study, 102 patients with relapsed or refractory HL were treated with two cycles of time-intensified DHAP, and responding patients under-

went ASCT.³⁴ The response rate was 89%, including a respectable 65% response rate in patients with primary progressive disease. No serious infections or treatment-related deaths occurred. PBSC collection was successful in 96% of patients. A subsequent report confirmed the high rate of successful stem cell collection with the DHAP regimen.³⁵

ASHAP (doxorubicin, methylprednisolone, high-dose cytarabine, cisplatin) is a modification of the above regimens that incorporates a continuous infusion of doxorubicin. Investigators at The University of Texas M. D. Anderson Cancer Center treated 56 patients, most of whom had relapsed after a MOPP (mechlorethamine, vincristine, procarbazine, prednisone)/ABVD hybrid regimen, with three cycles of ASHAP. Those with stable disease or better underwent subsequent ASCT. ORR to ASHAP was 70% (CR=34%, PR=36%), and 47 patients underwent ASCT. The 4-year EFS was 36%. Use of this regimen is limited by the current choice of ABVD as frontline therapy in most patients, with the need to minimize further anthracycline exposure.

Ifosfamide-containing Regimens

Investigators from Memorial Sloan-Kettering Cancer Center developed the ICE regimen (infusional ifosfamide, carboplatin, etoposide) to reduce the nonhematologic toxicities observed with cisplatin-containing regimens. As treatment for relapsed or refractory HL, ICE was administered every 2 weeks and stem cells were collected upon count recovery from the third cycle.³⁶ Patients with more than 25% reduction in tumor size proceeded to radiation/high-dose chemotherapy/ASCT. The ORR to ICE was 88% (CR=26%), and EFS for the entire treatment group was 58% at 43 months (68% for those who underwent ASCT). The median number of stem cells collected was 7×10^6 CD34+ cells/kg. A study of 100 patients with non-Hodgkin lymphoma (NHL) who were mobilized with ICE confirmed the effectiveness of this regimen for stem cell mobilization. In that study, 86% of patients collected more than 2×10^6 CD34+ cells/kg, and 61% collected more than 6×10^6 CD34+ cells/kg.³⁷

In the IVE regimen (ifosfamide, etoposide, epirubicin), the total doses of ifosfamide and etoposide are higher than those used in ICE (9 g/m² vs 5 g/m² and 600 mg/m² vs 300 mg/m², respectively). Retrospective and prospective studies demonstrate an ORR of 84–93% in HL patients treated with IVE^{38–40} and PFS of approximately 50% (includes patients who underwent ASCT). Like ICE, IVE is a very effective regimen for mobilization of PBSCs.^{40,41} Unfortunately, IVE is associated with severe hematotoxicity in the majority of patients, and a significant proportion of patients treated with this regimen require hospitalization for neutropenic fever or infection.

Gemcitabine-based Regimens

Newer salvage regimens for HL have incorporated the purine analog, gemcitabine (Gemzar, Eli Lilly), which lacks significant overlapping toxicity with other salvage agents and has a single-agent response rate of 20–40% in heavily pretreated HL patients.^{42–44} Based on preclinical studies that demonstrated the synergistic antilymphoma activity of gemcitabine and cisplatin,⁴⁵ regimens combining the two agents have been explored in several phase II studies. Gemcitabine, cisplatin, and methylprednisolone (GEM-P) was studied in 42 patients with relapsed or progressive lymphoma, including 17 patients with HL.⁴⁶ Neutropenia and thrombocytopenia were the most common toxicities, and 59% of patients had dose delays, primarily due to myelosuppression. However, serious nonhematologic toxicities were rare. The response rate among the HL patients was 82% (2 CRs and 12 PRs). All 9 patients who subsequently underwent stem cell harvesting had adequate collections to proceed with ASCT.

A retrospective analysis compared the outcomes of HL patients treated with gemcitabine, dexamethasone, and cisplatin (GDP) and those treated with mini-BEAM.⁴⁷ The response rate was 62% for GDP and 68% for mini-BEAM. Notably, target stem cell collection of more than 5×10^6 CD34+ cells/kg was achieved in 97% of patients treated with GDP, but only 57% of those treated with mini-BEAM. In addition, PFS at 1.5 years was significantly better with GDP (74% vs 35%).

The vinca alkaloid vinorelbine has single-agent activity in HL⁴⁸ and has been successfully combined with gemcitabine for the salvage treatment of HL. The combination of gemcitabine, vinorelbine, and liposomal doxorubicin (Doxil, Ortho Biotech; GVD) was evaluated by the Cancer and Leukemia Group B (CALGB) in a phase I/II trial.⁴⁹ In the phase I component, the maximum tolerated dose was found to be lower for patients who had a prior autotransplant. The ORR was 70% (CR=19%; PR=51%). EFS was 52% at 4 years for the 49 patients who did not have a history of prior autotransplant, 39 of whom went on to receive autotransplant after GVD. The median EFS for the 39 patients with prior autotransplant was considerably shorter (8.5 months). This outpatient regimen was generally well tolerated, with no deaths observed in transplant-naïve patients and a 7% incidence of febrile neutropenia.

Gemcitabine and vinorelbine also have been combined with ifosfamide in the IGEV regimen (ifosfamide, gemcitabine, vinorelbine, and prednisone). In a multi-institutional Italian study, 91 patients with relapsed or refractory HL were treated with four cycles of IGEV before proceeding to SCT.⁵⁰ Seventy-seven percent of patients had received only one prior regimen. The ORR was 81%, with a remarkable CR rate of 54%. Sixty-four

of 74 responding patients proceeded to ASCT, and 5 patients who had prior ASCT underwent nonmyeloablative allogeneic SCT. For the entire treatment group, 3-year PFS and OS were 53% and 70%, respectively. The regimen was administered in the outpatient setting. There were no treatment-related deaths and a low incidence of grade 3/4 toxicity. In a separate report, all 90 patients who had PBSCs mobilized and collected after 1–3 cycles of IGEV had a collection of more than 2×10^6 CD34+ cells/kg, with a median collection of 11×10^6 CD34+ cells/kg.⁵¹

The gemcitabine-containing regimens have demonstrated encouraging response rates and favorable toxicity profiles, and they can be considered for any patient with relapsed HL who has not yet been exposed to gemcitabine. However, the studies reported to date do not establish these regimens as superior to the more commonly used regimens, such as ESHAP and ICE. ICE remains our first choice of therapy for patients who relapse after ABVD because ICE contains non-crossresistant drugs, including an alkylator. The regimen also has an established track record of manageable toxicity and effective mobilization of PBSCs. Only randomized trials can conclusively demonstrate the superiority of one salvage regimen over another for patients with relapsed or refractory HL.

Therapy of Multiply Relapsed HL

Patients with HL who relapse after ASCT often continue to have chemosensitive disease, and they should be offered additional lines of chemotherapy. Many of the regimens discussed above can be effectively used in multiply relapsed patients, although dose adjustments may be required when a patient's bone marrow reserve has been compromised by prior high-dose chemotherapy.⁴⁹ Other options for palliative therapy are single-agent alkylators (oral chlorambucil or cyclophosphamide), vinblastine,⁵² and oral etoposide, even if patients have been exposed to these drugs previously. With additional courses of therapy, approximately 10% of patients will have prolonged survival after failing SCT.

Allogeneic Stem Cell Transplantation

Allogeneic SCT is a consideration for some patients with multiply relapsed or refractory HL. Enthusiasm for allogeneic SCT in this patient population has been hindered by treatment-related mortality (TRM) of 45–65%, due to infection, pulmonary complications, and graft-versus-host disease (GVHD).^{53–59} Reduced-intensity and nonmyeloablative conditioning regimens appear to decrease TRM, but longer follow-up is needed to accurately assess PFS and OS. Series of HL patients who underwent allogeneic SCT after a variety of reduced-intensity regimens

Table 1. Outcomes After Reduced-intensity Conditioning Versus Conventional Allogeneic Stem Cell Transplantation⁶⁶

	Conventional Conditioning, %	Reduced-intensity Conditioning, %	P
Acute GVHD	53	44	.05
Chronic GVHD at 1 year	33	38	NS
NRM at 3 months	28	15	.001
at 1 year	46	23	
Relapse	30	57	.04
5 year OS	22	28	.06
5 year PFS	20	18	NS

GVHD=graft-versus-host disease; NRM=nonrelapse mortality; NS=not significant; OS=overall survival; PFS=progression-free survival.

report TRM of 16–35%, PFS of 18–39%, and OS of 46–50%, at relatively short follow-up.^{60–65} In these patients, chemosensitivity prior to transplantation remained an important prognostic factor. The EBMT recently performed a retrospective comparison of myeloablative and reduced-intensity conditioning for 168 HL patients who underwent allogeneic SCT from 1997 to 2001 (Table 1).⁶⁶ Their results confirm that reduced-intensity conditioning is associated with lower TRM but a high relapse rate. In this patient population, prior ASCT and chemorefractory disease were significant poor prognostic factors for PFS and OS. Of note, the development of chronic GVHD was associated with a decreased risk of relapse, supporting the existence of a graft-versus-HL effect. Additional prospective studies are needed to establish which HL patients benefit from allogeneic SCT and to determine the optimal conditioning regimen and posttransplant immunosuppression for these patients.

New Agents

The CD30 antigen, a member of the tumor necrosis factor receptor family, has emerged as an attractive target for monoclonal antibody therapy of HL. CD30 is expressed by the malignant Reed-Sternberg (RS) cells in nearly all cases of classic HL, but it has limited expression in normal tissues. In a phase I study, the chimeric anti-CD30 antibody SGN-30 was administered to patients with multiply relapsed or refractory CD30+ malignancies.⁶⁷ SGN-30 was generally well tolerated, and the maximum tolerated dose was not reached when patients were treated with six weekly doses up to 12 mg/kg. There were no objective responses among the 21 patients with HL, although 4 had stable disease.

Similarly, no responses were observed in the first 16 evaluable patients treated with 6 or 12 mg/kg weekly doses of SGN-30 in a phase II trial.⁶⁸ The humanized anti-CD30 monoclonal antibody MDX-060 had modest activity in a phase I/II study. Two CRs and two PRs were observed in 63 HL patients, for an ORR of 6%.⁶⁹ Although single-agent activity has been disappointing in heavily pretreated patients, these anti-CD30 antibodies have minimal toxicity, and they may be more active earlier in the disease course, especially when combined with chemotherapy. Studies to test these hypotheses are ongoing, but one recent study combining an anti-CD30 antibody with gemcitabine-based chemotherapy was terminated early due to pulmonary toxicity. Research of combination therapy must thus proceed cautiously.

Antibody drug conjugates may be more effective for treatment of HL than the “naked” anti-CD30 antibodies. SGN-35 is an anti-CD30 antibody that is conjugated to the antitubulin agent monomethylauristatin E (MMAE). After binding to CD30 on the cell surface, SGN35 is internalized and MMAE is released via proteolytic degradation, leading to disruption of the microtubule network and apoptosis. SGN-35 has activity against HL in vitro and in vivo.⁷⁰ In a phase I trial of SGN-35, no dose-limiting toxicity was observed in the first 20 patients with CD30+ malignancies, including 18 patients with HL. Four patients met criteria for CR or PR and 9 had stable disease.⁷¹

Antibody therapy directed against the B-cell antigen CD20 may effectively treat a subset of patients with HL, perhaps by targeting the nonmalignant inflammatory infiltrate that supports the RS cells. Younes and associates treated 22 patients with relapsed HL with the anti-CD20 antibody, rituximab (Rituxan, Genentech/Biogen Idec);

22% responded, with a median response duration of 7.8 months.⁷² Notably, 6 of 7 patients had resolution of B symptoms. Rituximab has also been combined with gemcitabine for the treatment of relapsed HL, with responses observed in 48% of patients.⁷³ In these studies, response to rituximab has been limited to patients who have no extranodal disease.

Galiximab (Biogen Idec) is a primatized monoclonal antibody directed against CD80, an immune costimulatory molecule that regulates T-cell function. CD80 is constitutively expressed on some B-cell lymphomas, and it also has been identified on RS cells. Galiximab has demonstrated activity both as a single agent and in combination with rituximab for the treatment of follicular NHL,^{74,75} and it is being investigated by the CALGB as single-agent therapy for relapsed or refractory HL.

Novel agents that exert antitumor activity via proteasome inhibition, epigenetic mechanisms, or immune modulation have proven to be effective therapies for a number of hematologic malignancies; several of these agents are now being studied for the treatment of relapsed HL. The proteasome inhibitor bortezomib (Velcade, Millennium) demonstrated activity against HL-derived cell lines *in vitro*,⁷⁶ however, no HL patients responded in clinical trials.^{77,78} Histone deacetylase inhibitors, which can regulate aberrant gene expression in malignant cells via changes in chromatin structure, are also being explored for the treatment of HL. In a phase II trial of the histone deacetylase inhibitor MGCD0103, 5 of the first 7 evaluable HL patients, all of whom had relapsed after ASCT, had tumor reduction ranging from 21% to 70%.⁷⁹ The immunomodulatory agents thalidomide (Thalomid, Celgene) and lenalidomide (Revlimid, Celgene) are generally well-tolerated oral drugs that may exert antilymphoma activity in HL by modulating the inflammatory infiltrate surrounding the RS cells or by blocking angiogenesis. Thalidomide in combination with vinblastine had a response rate of 36% in a small phase II study of heavily pretreated HL patients.⁸⁰ Trials of lenalidomide are ongoing.

Conclusions

ASCT remains the standard of care for HL patients who relapse after or are refractory to primary chemotherapy, and approximately half of patients with chemosensitive HL can be cured with this approach. There are many effective salvage chemotherapy regimens incorporating non-crossresistant agents, and the pretransplant regimen should be chosen to maximize response and minimize toxicity. Patients who relapse after ASCT often continue to have chemosensitive disease, but their curative options are limited. Reduced-intensity allogeneic SCT can be considered for some patients with multiply relapsed HL,

but more investigation is required to determine the optimal conditioning regimen and posttransplant management. Patients with chemoresistant HL respond poorly to SCT. Fortunately, many new agents are in development for the treatment of relapsed HL, and any patient who fails ASCT should be considered for participation in a clinical trial.

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