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Accelerated Total Lymphoid Irradiation -containing Salvage Regimen for Patients with Refractory and Relapsed Hodgkin Lymphoma: 20 Years of Experience

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Abstract

Purpose—We report the long-term results of integrated accelerated involved-field radiotherapy (IFRT) followed by total lymphoid irradiation (TLI) as part of the high-dose salvage regimen followed by autologous bone marrow transplantation (ABMT) or autologous stem-cell transplantation (ASCT) in patients with relapsed or refractory Hodgkin lymphoma (HL).

Methods and Materials—From 11/1985 to 07/2008, 186 previously unirradiated patients with relapsed/refractory HL underwent salvage therapy on four consecutive IRB-approved protocols. All patients had biopsy-proven primary refractory or relapsed HL. After standard-dose salvage chemotherapy (SC), accelerated IFRT (18–20 Gy) was given to relapsed/refractory sites, followed by TLI (15–18 Gy) and high-dose chemotherapy (HDT). Overall survival (OS) and event-free survival (EFS) were analyzed by Cox analysis and disease-specific survival (DSS) by competing risk regression.

Results—With a median follow-up of 57 months among survivors, 5- and 10-year OS was 68% and 56%, 5- and 10-year EFS was 62% and 56%, and 5- and 10-year cumulative incidence of HL-related deaths was 21% and 29%, respectively. On multivariable analysis, complete response (CR)

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All authors have materially participated in the research and/or article preparation. Dr. Andreas Rimner and Dr. Joachim Yahalom designed the research project, supervised data collection, interpreted the data, and wrote the manuscript. Shona Lovie, Monica Chelius and Karen Chau collected, edited, and analyzed data and assisted in editing the manuscript. Meier Hsu and Dr. Zhigang Zhang performed statistical analyses and made tables and figures. Dr. Alison Moskowitz, Dr. Matthew Matasar, and Dr. Craig Moskowitz contributed to data interpretation and writing the manuscript. All authors have approved the final article.

to SC was independently associated with improved OS and EFS. Primary refractory disease and extranodal disease were independently associated with poor DSS. Eight patients had grade 3 cardiac toxicity with 3 deaths. Ten patients developed second malignancies, five of whom died.

Conclusion—Accelerated IFRT followed by TLI and HDT is an effective, feasible, and safe salvage strategy for patients with relapsed/refractory HL with excellent long-term OS, EFS, and DSS. CR to SC is the most important prognostic factor.

Keywords

Hodgkin lymphoma; early stage; relapse; transplantation; high-dose therapy; radiotherapy

Introduction

Newly diagnosed Hodgkin lymphoma (HL) is treated with chemotherapy with or without radiation therapy (RT) resulting in long-term failure-free survival of 60% for advanced stages^{1–5} and 90% for early stages.^{6–8} For relapsed/refractory HL, salvage options include chemotherapy alone, RT alone, combined modality treatment (CMT), and autologous or allogeneic bone marrow transplantation.⁹ Up to 83% of first-line failures after chemotherapy alone occur in the same sites of initial disease involvement.^{10,11} Salvage RT has been shown to result in complete response (CR) rates of up to 93%.^{12–18} The largest study found that salvage RT to a median dose of 40 Gy at first relapse resulted in a CR rate of 77%, 5-year freedom from second failure (FF2F) of 28%, and 5-year overall survival (OS) of 51%, respectively.¹⁹ CMT has been associated with even better outcomes and is thus preferred over RT as salvage monotherapy.¹⁴

By now, autologous stem cell transplantation (ASCT) is widely considered standard of care for patients who are medically fit, since two randomized trials showed improvement in failure-free survival with ASCT.^{20–22} Recently, the addition of brentuximab vedotin as maintenance therapy after transplantation has been shown to result in improved progression-free survival (PFS).²³ If patients relapse again after ASCT, outcomes are dismal with only 23% of patients surviving,²⁴ and median survival times of 24–33 months.^{25,26} Thus, optimizing salvage treatment for patients with relapsed/refractory HL represents the best chance for cure.

After salvage ASCT without integrated RT, most failures still occur in formerly involved sites.²⁷ With integrated involved field radiation therapy (IFRT), most relapses after ASCT have been observed in lymph nodes adjacent to previously involved sites or new nodal sites.²⁸ To avoid such failures, total lymphoid irradiation (TLI) was developed. Accelerated hyperfractionated TLI as part of the consolidative regimen preceding ASCT (1500cGy in 10 fractions twice daily with a boost of an additional 1500cGy in 10 fractions) compared to salvage chemotherapy alone has been shown to result in 5-year event-free survival (EFS) of 63% vs 6% [$p<0.0001$] and 5-year OS of 61% vs 27% [$p=0.04$].²⁹

Since 1985 we have incorporated TLI as a standard component of salvage therapy for previously unirradiated patients with relapsed/refractory HL. Shortly after SC, we deliver TLI in a hyperfractionated regimen twice daily to minimize interference of RT with HDT,

prevent unnecessary delays proceeding with ASCT, guarantee complete RT delivery without delays due to potential complications from HDT/ASCT, and avoid potential exposure of newly engrafted and radiosensitive stem cells to ionizing RT. We present the analysis of 186 patients treated with TLI at our institution.

Methods and Materials

Patient and Treatment Characteristics

From 11/1985 to 07/2008, 186 previously unirradiated patients with relapsed/refractory HL were uniformly treated with TLI (see CONSORT diagram, Supplementary Figure 1) on one of four institutional review board (IRB)-approved salvage therapy protocols at our institution.^{30–33} All four protocols focused on salvage and consolidation therapy followed by autologous bone marrow transplant (ABMT)/ASCT for patients with relapsed/refractory HL (see salvage treatment algorithm, Supplementary Figure 2). Inclusion criteria were uniform across all four protocols; all patients had to have failed after conventional anthracycline-based first-line therapy, with pathologic confirmation of relapsed/refractory disease at our institution. The first protocol (1985–1994) explored various salvage therapies: pre-transplant IFRT followed by TLI, Cytosan/VP-16 (CV)/Cytosan/BCNU/VP-16 (CBV) and ABMT. The second protocol (1994–1998) introduced ifosfamide/carboplatin/etoposide (ICE) as the standard SC followed by pre-transplant IFRT, TLI, CV/CBV and ABMT or ASCT (starting in 1995). The third protocol (1998–2004) followed the same regimen as the second protocol, but the choice of SC (either standard or augmented ICE) was based on a patient's risk category from a three-factor risk model using duration of remission <1 year, B-symptoms, and extranodal disease at relapse (category 1: 0–1 risk factors; category 2: 2 risk factors; category 3: 3 risk factors).³² The fourth protocol (2004–2008) followed the same risk model, and additionally required FDG-avid, measurable disease at study entry, minimal disease state prior to ASCT and added gemcitabine/vinorelbine/liposomal doxorubicin (GND) in patients with persistent FDG-avidity. Prior to 1995, patients underwent bone marrow transplantation for stem cell rescue; subsequently, peripheral stem cell mobilization and transplantation has been standard. Since 1998, patients eligible for ASCT at our institution have been treated with risk-adapted salvage therapy.

Disease-related data from 186 consecutive patients were prospectively collected and retrospectively confirmed by review of electronic medical records after obtaining IRB approval. All 186 patients completed both salvage and consolidative regimen and underwent ABMT/ASCT. Patients were followed and imaged following institutional guidelines.

The salvage RT treatment algorithm was as follows: two cycles of SC, repeat imaging to determine residual disease, conditioning consisting of accelerated IFRT (1.8 Gy × 10 fractions twice daily; median dose: 18 Gy; interquartile range [IQR]: 15 to 18 Gy) to sites of relapsed/refractory disease in 174 patients (94%), followed by TLI (1.8 Gy × 10 fractions twice daily; median dose: 18 Gy; IQR 18 Gy to 20.04 Gy) and HDT (typically high-dose cyclophosphamide and etoposide). Integrated IFRT/TLI was delivered twice daily to allow rapid completion of the entire treatment within 10 days. This approach minimized interference of RT with HDT and prevented unnecessary delays in proceeding with transplant. Patients were typically admitted between IFRT and TLI one week prior to

transplant for maximal supportive care during TLI and HDT. Patients were treated with 2D conventional fields AP/PA, planned on CT imaging since 1996. Three patients received incomplete radiation therapy prior to salvage treatment and were deemed eligible for TLI. Detailed RT records including treatment dates, dose, fractionation, and fields were available.

Endpoints

The primary objective was to determine the long-term outcome of patients treated with integrated TLI. OS and DSS were determined by the date of either death due to any cause or disease, or the date of last follow-up. EFS was determined by time to progression of disease, second malignancy, death due to any cause (whichever occurred first), or the date of last follow-up. To minimize incomplete mortality data we matched our information with the Social Security Death Index and National Death Index. The secondary objective was to identify factors associated with patient outcomes. Response rates to initial treatment, salvage treatment, and transplantation were measured as defined by the revised response criteria for malignant lymphoma.³⁴ Early, transplantation-related toxicity was defined as occurring 100 days post-transplantation, and late morbidity >100 days post-transplantation,^{35,36} and scored according to the Common Terminology Criteria for Adverse Events (CTCAE, version 3.0) (<http://ctep.cancer.gov>). Data on second malignancies were collected from chart review and institutional tumor registry. Patterns of failure after transplantation were analyzed and reviewed for their relationship to radiation fields. Relapses post-transplant were scored in-field, out-of-field, or both.

Statistical Analysis

All follow-up and outcome data were calculated from the time of transplantation. OS and EFS rates were calculated by the Kaplan-Meier product-limit method.³⁷ Comparisons of survival curves were performed using the log-rank test.³⁸ DSS, accounting for death due to causes other than HL as a competing factor, was calculated as a cumulative incidence rate and compared by methods of competing risk.³⁹

Cox regression models were used to analyze the association of patient, disease and treatment factors at initial diagnosis and relapsed/refractory disease identification with OS and EFS endpoints, while competing risk regression was used for the DSS endpoint. All factors with univariate p-values <0.2 were entered into a multivariable model and a step-wise selection method was implemented to reduce the model until only those predictors with a p-value <0.05 remained.⁴⁰ A similar method utilizing backwards selection was performed for DSS analysis. Competing risk analysis was performed using *crr* and *cuminc* functions in library *cmprsk* of R software version 2.3. All other statistical analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

Results

Patient and disease characteristics

The clinical, pathologic, and treatment parameters of the patient cohort are described in Table 1. One hundred eleven patients (60%) presented initially with advanced disease, while 90 (48%) had advanced disease at the time of relapse. Sixty-four patients (34%) had

extranodal disease at diagnosis, and 48 (26%) had extranodal disease at relapse. Ninety-eight (53%) had primary refractory HL, and 88 (47%) relapsed after CR to chemotherapy alone (58% of those relapsed in <1 year). One hundred two patients (55%) achieved a CR in response to salvage therapy. Median age at transplantation was 30 years (range 12 to 66 years). 37.5% underwent ABMT, 60% a peripheral ASCT since its introduction in 1995, and 3% (5 patients) had a tandem autotransplantation.

Survival and cumulative incidence of HL-specific deaths

At time of last follow-up, 116 patients (62%) were alive with no evidence of disease, and 65 patients had died. Median follow-up was 57 months among survivors (range 4–233). The median OS was 13 years, with a 5- and 10-year OS of 68% and 56%, respectively (Figure 1a). OS marginally improved after the introduction of peripheral ASCT in 1995 (HR 0.53, $p=0.02$); improvement in OS was also observed after initiation of risk-adapted salvage HDT in 1998 (HR 0.52, $p=0.02$) (Table 2). Since 1998, only one death (1.2%) from transplant-related mortality has occurred.

Seventy-six events (progression of disease, second malignancy, or death from any cause) were registered. The median EFS was 12 years, with 5- and 10-year EFS of 62% and 56%, respectively (Figure 1b).

To date, 38 patients have died of HL, and the 5- and 10-year cumulative incidence of HL-related deaths was 21% and 29%, respectively (Figure 1c). Of note, 61% of HL-related deaths occurred within the first 3 years. Thirteen of the HL-related deaths occurred over the subsequent 4 years, and no death occurred more than 9 years post ASCT.

Association of factors with OS, EFS, and DSS

On univariate analysis, the association between CR to SC and improved OS was highly significant with a hazard ratio (HR) of 0.33 (95% CI 0.19 to 0.57; $p<0.0001$) (Figure 2a; Table 2). Similarly, CR to SC was significantly associated with improvement in EFS (HR 0.34 (95% CI 0.21 to 0.56; $p<0.0001$)) (Figure 2b; Table 3), as well as DSS (HR 0.49 (95% CI 0.25 to 0.94; $p=0.04$)) (Figure 2c; Table 4).

Relapsed HL compared to primary refractory HL was significantly associated with improved OS (HR 0.6; $p=0.05$) (Table 2), EFS (HR 0.53; $p=0.007$) (Table 3), and lower cumulative incidence of HL-specific deaths (HR 0.36; $p=0.004$) (Table 4) (Supplementary Figure 3).

Patients with extranodal disease prior to SC were at significantly higher risk for HL-specific death (HR 2.12; $p=0.02$) (Table 4) and at borderline elevated risk for an event (progression of disease, second malignancy, or death of any cause) (HR 1.6; $p=0.05$) (Table 3) (Supplementary Figure 4). OS was not significantly associated with extranodal disease at relapse (Table 2).

Additional factors associated with OS included CR to initial therapy (HR 0.59; $p=0.04$) (Table 2). Bulky disease (>5cm) at diagnosis (HR 1.89; $p=0.05$) and score of 3 compared to 1 in our three-factor risk model (HR 2.24; $p=0.02$) were associated with inferior OS (Table 2). Transplantation after introduction of ASCT in 1995 (HR 0.53; $p=0.02$), and

transplantation after introduction of risk-stratified salvage therapy in 1998 (HR 0.52; $p=0.02$) were associated with improved OS (Table 2).

CR to initial therapy was associated with improved EFS (HR 0.52; $p=0.006$). A score of 3 in the three-factor risk model (HR 2.64; $p=0.004$) and advanced stage at recurrence (HR 1.63; $p=0.04$) were associated with inferior EFS (Table 3). Bulky disease ($>5\text{cm}$) at diagnosis (HR 1.67; $p=0.07$), and B-symptoms at relapse (HR 1.56; $p=0.06$) were borderline associated with decreased EFS (Table 3).

Higher cumulative incidence of HL-specific deaths was significantly associated with bulky disease ($>5\text{cm}$) at diagnosis (HR 2.43; $p=0.03$), and score of 3 in the three-factor risk model (HR 3.48; $p=0.001$) (Table 4). CR to initial therapy (HR 0.31; $p=0.003$), and CR to SC (HR 0.49; $p=0.04$) were associated with improved DSS (Table 4).

On multivariate analysis, only CR to SC remained associated with improved OS (HR 0.33; $p<0.0001$) and EFS (HR 0.37; $p<0.0001$) (Table 2). Relapsed disease remained associated with improved EFS (HR 0.59; $p=0.03$) (Table 3) and DSS (HR 0.38; $p=0.01$) (Table 4) when compared to primary refractory disease. Extranodal disease at relapse continued to be associated with worse DSS (HR 1.97; $p=0.04$) (Table 4).

Patterns of failure

There were 51 failures after salvage therapy and transplantation. Detailed information about failure sites was available for 40 patients. Thirty-four failures occurred in the TLI field (22 failures inside and 17 outside the IFRT boost field). Most failures inside the IFRT boost fields occurred rapidly after salvage therapy and transplantation, suggesting primary resistance to salvage therapy. Six failures occurred exclusively outside any irradiated areas, and 15 failures occurred both in- and outside the TLI fields. Extranodal failures occurred in 28 patients, mostly in the lungs, liver and bones (details listed in Supplementary Table 1).

Morbidity and secondary malignancies

The most common grade 3 or higher early toxicities from treatment were infections (58%), mucositis (22%), pulmonary (18%), and others (16%) (Supplementary Table 2). Most early toxicities resolved without sequelae. The most common grade 3 late toxicities were infections (6%), pulmonary (6%), gastrointestinal (5%), cardiac (4%), and others (4%) (Supplementary Table 3). Eight patients had late grade 3 cardiac toxicity; 3 of them died.

Ten patients (5%) developed second malignancies: 5 hematologic malignancies (2x acute myeloid leukemia, 1 myelodysplastic syndrome, 1 diffuse large B-cell lymphoma involving the liver, 1 non-Hodgkin lymphoma (site unknown)), and 5 with solid malignancies (papillary thyroid cancer (in-field), lung (site unknown), greater curvature of the stomach (relation to RT field difficult to assess), colon (site unknown), and unknown primary carcinoma, most likely lung carcinoma with widespread involvement of the mediastinum and retroperitoneum (in-field)); 5 patients died of their second malignancy.

Discussion

Overall outcome

This study is, to our knowledge, the largest reported long-term experience with systematic integration of TLI into salvage therapy for relapsed/refractory HL. We found excellent long-term OS, EFS, and HL-specific deaths at 68%, 62% and 21% by 5 years and 56%, 56% and 29% by 10 years, respectively. This is comparable to results of the TLI/chemotherapy arm by Evens et al (n=32) who reported a 5-year OS and EFS of 63% and 61%, respectively.²⁹ Others reported 5-year PFS of 41–48% and OS of 54–57%, respectively, after ABMT or ASCT.⁴¹ Between 10% and 29% of patients in these studies received RT, mostly total body irradiation.^{35,36,42,43} In a highly selected subgroup of patients with complete remission for at least 2 years post-ASCT, a 10-year OS of 77% was reported by Majhail et al.⁴⁴

Predictive factors

In the largest retrospective study to date, the German Hodgkin Lymphoma Study Group identified duration of initial remission, stage of disease at relapse, and anemia as the 3 most important prognostic factors for additional relapses after failing initial therapy.⁴⁶ However, only one-third (140/422) of these patients underwent ASCT/ABMT as part of their salvage therapy.

Josting et al. reported outcomes after salvage RT alone. B-symptoms and stage at relapse were prognostic factors for OS, Karnofsky Performance Status was prognostic for 5-year FF2F, and duration of first remission was prognostic for 5-year FF2F in limited-stage patients. However, RT fields and dose varied significantly and subsequent treatment was heterogeneous, including ASCT, chemotherapy, repeat RT, and palliative treatment.²³

Response to SC has been reported as one of the most important predictive factors for EFS, PFS, and OS.^{33,35,43,47–49} CR to SC as measured by PET imaging has been associated with improved OS.^{50,51} In our study, we found a 5-year OS and EFS of 48% and 44% for patients with less than a CR to standard SC, respectively. In contrast, the 5-year OS and EFS for patients who achieved a CR to standard SC was 79% and 72%, respectively.

We previously developed a prognostic model, where B-symptoms, extranodal disease, and a relapse interval of <12 months were associated with worse EFS and OS after ASCT.³¹ In this analysis, however, B-symptoms were not confirmed as a predictive factor on multivariable analysis, extranodal disease remained significant only for DSS, and relapsed vs refractory HL was significant for EFS and DSS. The most significant factor associated with both OS and EFS was CR to standard SC.

Other predictive factors for worse prognosis that have been previously reported include extranodal disease^{41,47,52}, higher number of prior chemotherapy regimens and relapses^{35,41,47}, presence of B-symptoms^{43,48,49,52}, disseminated bone marrow involvement⁴⁸, relapse in a previously irradiated field⁴¹, nodular sclerosing histology⁵², and poor performance status⁵². Because of the negative impact of higher number of relapses, we offer salvage ASCT to most patients at first relapse.

The AETHERA trial, a multicenter randomized phase 3 trial, showed a PFS benefit of early consolidation with the addition of brentuximab vedotin (42.9 months) vs placebo (24.1 months) after ASCT in patients at high-risk for relapse (defined as primary refractory HL, relapsed HL within <12 months, or extranodal involvement prior to pre-transplant SC).¹³ Only 7% of patients received RT as part of the ASCT conditioning regimen. The impressive PFS benefit with the addition of brentuximab may require adjustments in the integration and patient selection for TLI. However, the optimal definition of a high-risk patient population that will benefit most from consolidation therapy remains to be determined.⁴⁵

Second malignancies and morbidity

We found the most common second malignancies after ASCT to be mainly lymphoproliferative and hematologic malignancies. Because the risk for second malignancies is multifactorial due to the combination of chemotherapy, RT, ASCT, growth factors and immunosuppression, it is impossible to determine the proportion of second malignancies specifically due to TLI. We attempted to correlate sites of solid second malignancies with RT fields but were limited by the lack of information on the specific tumor location and small numbers. Previous reports found no significant difference between patients treated with ASCT (35% received RT) when compared to conventional salvage therapy (62% received RT).⁵³ In a matched control study, Andre et al. observed a similar incidence of secondary myelodysplasia or acute myeloid leukemia with ASCT compared to conventional chemotherapy, while the risk for solid tumors was increased with HDT and ASCT.⁵⁴ The relatively low incidence of solid malignancies in our subset may be explained by the relatively short median follow-up of 57 months, as the median time from ASCT to second malignancy is approximately 9 years.⁵⁵

The strengths of our study include its large size, systematic integration of TLI in our salvage therapy regimen, consistent dose, fractionation, and RT field design over a long period of time, and systematic patient follow up. The limitations include the lack of randomization which would allow determination of the impact of TLI specifically rather than TLI as part of a salvage regimen, some heterogeneity of patients and management over the long time period (i.e. ABMT/ASCT, change in SC, risk adapted use of ICE).

Conclusion

Integrating accelerated IFRT followed by TLI into HDT salvage for previously unirradiated patients with relapsed/refractory HL is effective, feasible, and safe. It resulted in excellent long-term OS, EFS, and DSS in a heavily pretreated patient population. On multivariate analysis, CR to standard dose SC was independently associated with improved long-term OS and EFS after HDT. Primary refractory disease and extranodal disease at relapse were found to be associated with worse outcome. The long-term morbidity and second malignancy rates were relatively low and mostly occurred in the early post-transplantation period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Aleman BMP, Raemaekers JMM, Tirelli U, et al. Involved-field radiotherapy for advanced Hodgkin's lymphoma. *New England Journal of Medicine*. 2003; 348(24):2396–2406. [PubMed: 12802025]
2. Canellos GP, Anderson JR, Propert KJ, et al. Chemotherapy of advanced Hodgkin's disease with MOPP, ABVD, or MOPP alternating with ABVD. *New England Journal of Medicine*. 1992; 327(21):1478–1484. [PubMed: 1383821]
3. Connors JM, Klimo P, Adams G, et al. Treatment of advanced Hodgkin's disease with chemotherapy - Comparison of MOPP/ABV hybrid regimen with alternating courses of MOPP and ABVD: A report from the National Cancer Institute of Canada Clinical Trials Group. *Journal of Clinical Oncology*. 1997; 15(4):1638–1645. [PubMed: 9193364]
4. Duggan DB, Petroni GR, Johnson JL, et al. Randomized comparison of ABVD and MOPP/ABV hybrid for the treatment of advanced Hodgkin's disease: Report of an Intergroup trial. *Journal of Clinical Oncology*. 2003; 21(4):607–614. [PubMed: 12586796]
5. Edwards-Bennett SM, Jacks LM, Moskowitz CH, et al. Stanford V program for locally extensive and advanced Hodgkin lymphoma: the Memorial Sloan-Kettering Cancer Center experience. *Ann Oncol*. Sep 16.2009
6. Bonadonna G, Bonfante V, Viviani S, Di Russo A, Villani F, Valagussa P. ABVD plus subtotal nodal versus involved-field radiotherapy in early-stage Hodgkin's disease: Long-term results. *Journal of Clinical Oncology*. 2004; 22(14):2835–2841. [PubMed: 15199092]
7. Engert A, Franklin J, Eich HT, et al. Two cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine plus extended-field radiotherapy is superior to radiotherapy alone in early favorable Hodgkin's lymphoma: Final results of the GHSG HD7 trial. *Journal of Clinical Oncology*. 2007; 25(23):3495–3502. [PubMed: 17606976]
8. Meyer RM, Gospodarowicz MK, Connors JM, et al. Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *Journal of Clinical Oncology*. 2005; 23(21):4634–4642. [PubMed: 15837968]
9. NCCN Clinical practice guidelines in oncology. 2016 v.3.2016.
10. Poen JC, Hoppe RT, Horning SJ. High-dose therapy and autologous bone marrow transplantation for relapsed/refractory Hodgkin's disease: The impact of involved field radiotherapy on patterns of failure and survival. *International Journal of Radiation Oncology Biology Physics*. 1996; 36(1):3–12.
11. Macdonald DA, Ding K, Gospodarowicz MK, et al. Patterns of disease progression and outcomes in a randomized trial testing ABVD alone for patients with limited-stage Hodgkin lymphoma. *Annals of Oncology*. 2007; 18(10):1680–1684. [PubMed: 17846017]
12. Brada M, Eeles R, Ashley S, Nichols J, Horwich A. Salvage radiotherapy in recurrent Hodgkin's disease. *Annals of Oncology*. 1992; 3(2):131–135. [PubMed: 1606082]
13. Leigh BR, Fox KA, Mack CF, Baier M, Miller TP, Cassady JR. Radiation therapy salvage of Hodgkin's disease following chemotherapy failure. *International Journal of Radiation Oncology Biology Physics*. 1993; 27(4):855–862.

14. Uematsu M, Tarbell NJ, Silver B, et al. Wide-field radiation therapy with or without chemotherapy for patients with Hodgkin disease in relapse after initial combination chemotherapy. *Cancer*. 1993; 72(1):207–212. [PubMed: 7685241]
15. Pezner RD, Lipsett JA, Vora N, Forman SJ. Radical radiotherapy as salvage treatment for relapse of Hodgkin's disease initially treated by chemotherapy alone: Prognostic significance of the disease-free interval. *International Journal of Radiation Oncology Biology Physics*. 1994; 30(4): 965–970.
16. Wirth A, Corry J, Laidlaw C, Matthews J, Liew KH. Salvage radiotherapy for Hodgkin's disease following chemotherapy failure. *International Journal of Radiation Oncology Biology Physics*. 1997; 39(3):599–607.
17. Josting A, Nogová L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Lymphoma Study Group. *Journal of Clinical Oncology*. 2005; 23(7):1522–1529. [PubMed: 15632410]
18. Campbell B, Wirth A, Milner A, Di Iulio J, MacManus M, Ryan G. Long-term follow-up of salvage radiotherapy in Hodgkin's lymphoma after chemotherapy failure. *International Journal of Radiation Oncology Biology Physics*. 2005; 63(5):1538–1545.
19. Josting A, Nogová L, Franklin J, et al. Salvage radiotherapy in patients with relapsed and refractory Hodgkin's lymphoma: A retrospective analysis from the German Hodgkin Lymphoma Study Group. *Journal of Clinical Oncology*. 2005; 23(7):1522–1529. [PubMed: 15632410]
20. Schmitz N, Pfistner B, Sextro M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: A randomised trial. *Lancet*. 2002; 359(9323):2065–2071. [PubMed: 12086759]
21. Linch DC, Winfield D, Goldstone AH, et al. Dose intensification with autologous bone-marrow transplantation in relapsed and resistant Hodgkin's disease: Results of a BNLI randomised trial. *Lancet*. 1993; 341(8852):1051–1054. [PubMed: 8096958]
22. Schmitz N, Haverkamp H, Josting A, et al. Long term follow up in relapsed Hodgkin's disease (HD): updated results of the HD-R1 study comparing conventional chemotherapy (cCT) to high-dose chemotherapy (HDCT) with autologous haemopoietic stem cell transplantation (ASCT) of the German Hodgkin Study Group (GHSG) and the Working Party Lymphoma of the European Group for Blood and Marrow Transplantation (EBMT). *Journal of Clinical Oncology*, 2005 ASCO Annual Meeting Proceedings. Jun 1. 2005 23(16S, Part I of II):6508. Supplement.
23. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*. 2015; 385(9980):1853–1862.
24. Moskowitz AJ, Perales MA, Kewalramani T, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. *British Journal of Haematology*. 2009; 146(2):158–163. [PubMed: 19438504]
25. Crump M. Management of Hodgkin lymphoma in relapse after autologous stem cell transplant. *Hematology/the Education Program of the American Society of Hematology*. American Society of Hematology. Education Program. 2008:326–333.
26. Kewalramani T, Nimer SD, Zelenetz AD, et al. Progressive disease following autologous transplantation in patients with chemosensitive relapsed or primary refractory Hodgkin's disease or aggressive non-Hodgkin's lymphoma. *Bone Marrow Transplantation*. 2003; 32(7):673–679. [PubMed: 13130314]
27. Mundt AJ, Sibley G, Williams S, Hallahan D, Nautiyal J, Weichselbaum RR. Patterns of failure following high-dose chemotherapy and autologous bone marrow transplantation with involved field radiotherapy for relapsed/refractory Hodgkin's disease. *International Journal of Radiation Oncology Biology Physics*. 1995; 33(2):261–270.
28. Mundt AJ, Connell PP, Mansur DB. What is the optimal treatment volume in Hodgkin's disease patients undergoing high-dose chemotherapy and adjuvant radiation therapy? *Radiation Oncology Investigations*. 1999; 7(6):353–359. [PubMed: 10644058]

29. Evens AM, Altman JK, Mittal BB, et al. Phase I/II trial of total lymphoid irradiation and high-dose chemotherapy with autologous stem-cell transplantation for relapsed and refractory Hodgkin's lymphoma. *Annals of Oncology*. 2007; 18(4):679–688. [PubMed: 17307757]
30. Yahalom J, Gulati SC, Toia M, et al. Accelerated hyperfractionated total-lymphoid irradiation, high-dose chemotherapy, and autologous bone marrow transplantation for refractory and relapsing patients with Hodgkin's disease. *Journal of Clinical Oncology*. 1993; 11(6):1062–1070. [PubMed: 8501492]
31. Moskowitz CH, Nimer SD, Zelenetz AD, et al. A 2-step comprehensive high-dose chemoradiotherapy second-line program for relapsed and refractory Hodgkin disease: Analysis by intent to treat and development of a prognostic model. *Blood*. 2001; 97(3):616–623. [PubMed: 11157476]
32. Moskowitz C. Risk-adapted therapy for relapsed and refractory lymphoma using ICE chemotherapy. *Cancer Chemotherapy and Pharmacology, Supplement*. 2002; 49(7)
33. Moskowitz CH, Kewalramani T, Nimer SD, Gonzalez M, Zelenetz AD, Yahalom J. Effectiveness of high dose chemoradiotherapy and autologous stem cell transplantation for patients with biopsy-proven primary refractory Hodgkin's disease. *British Journal of Haematology*. 2004; 124(5):645–652. [PubMed: 14871252]
34. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology*. 2007; 25(5):579–586. [PubMed: 17242396]
35. Sureda A, Arranz R, Iriando A, et al. Autologous stem-cell transplantation for Hodgkin's disease: Results and prognostic factors in 494 patients from the Grupo Español de Linfomas/Transplante Autólogo de Médula Ósea Spanish Cooperative Group. *Journal of Clinical Oncology*. 2001; 19(5):1395–1404. [PubMed: 11230484]
36. Lazarus HM, Loberiza FR, Zhang MJ, et al. Autotransplants for Hodgkin's disease in first relapse or second remission: A report from the autologous blood and marrow transplant registry (ABMTR). *Bone Marrow Transplantation*. 2001; 27(4):387–396. [PubMed: 11313668]
37. Kaplan ELMP. Nonparametric estimation from incomplete observations. *J Am Statist Assoc*. 1958; 53:457–481.
38. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep*. Mar; 1966 50(3):163–170. [PubMed: 5910392]
39. Gray R. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat*. 1988; 16:1141–1154.
40. Cox DR. Regression model and life-tables. *J Roy Statist Soc Ser B*. 1972; 34:187–220.
41. Stiff PJ, Unger JM, Forman SJ, et al. The value of augmented preparative regimens combined with an autologous bone marrow transplant for the management of relapsed or refractory Hodgkin disease: A Southwest Oncology Group phase II trial. *Biology of Blood and Marrow Transplantation*. 2003; 9(8):529–539. [PubMed: 12931122]
42. Morschhauser F, Brice P, Fermé C, et al. Risk-adapted salvage treatment with single or tandem autologous stem-cell transplantation for first relapse/refractory Hodgkin's lymphoma: Results of the prospective multicenter H96 trial by the GELA/SFGM study group. *Journal of Clinical Oncology*. 2008; 26(36):5980–5987. [PubMed: 19018090]
43. Majhail NS, Weisdorf DJ, Defor TE, et al. Long-term results of autologous stem cell transplantation for primary refractory or relapsed Hodgkin's lymphoma. *Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation*. 2006; 12(10):1065–1072.
44. Majhail NS, Bajorunaite R, Lazarus HM, et al. Long-term survival and late relapse in 2-year survivors of autologous haematopoietic cell transplantation for Hodgkin and non-Hodgkin lymphoma. *British Journal of Haematology*. 2009; 147(1):129–139. [PubMed: 19573079]
45. Engert A. Hodgkin's lymphoma: who needs consolidation treatment? *Lancet*. May 9; 2015 385(9980):1810–1812. [PubMed: 25796457]
46. Josting A, Franklin J, May M, et al. New prognostic score based on treatment outcome of patients with relapsed Hodgkin's lymphoma registered in the database of the German Hodgkin's Lymphoma Study Group. *Journal of Clinical Oncology*. 2002; 20(1):221–230. [PubMed: 11773173]

47. Brice P, Bouabdallah R, Moreau P, et al. Prognostic factors for survival after high-dose therapy and autologous stem cell transplantation for patients with relapsing Hodgkin's disease: Analysis of 280 patients from the French registry. *Bone Marrow Transplantation*. 1997; 20(1):21–26. [PubMed: 9232251]
48. Horning SJ, Chao NJ, Negrin RS, et al. High-dose therapy and autologous hematopoietic progenitor cell transplantation for recurrent or refractory Hodgkin's disease: Analysis of the Stanford University results and prognostic indices. *Blood*. 1997; 89(3):801–813. [PubMed: 9028311]
49. Yuen AR, Rosenberg SA, Hoppe RT, Halpern JD, Horning SJ. Comparison between conventional salvage therapy and high-dose therapy with autografting for recurrent or refractory Hodgkin's disease. *Blood*. 1997; 89(3):814–822. [PubMed: 9028312]
50. Svoboda J, Andreadis C, Elstrom R, et al. Prognostic value of FDG-PET scan imaging in lymphoma patients undergoing autologous stem cell transplantation. *Bone Marrow Transplantation*. 2006; 38(3):211–216. [PubMed: 16770314]
51. Castagna L, Bramanti S, Balzarotti M, et al. Predictive value of early 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) during salvage chemotherapy in relapsing/refractory Hodgkin lymphoma (HL) treated with high-dose chemotherapy. *British Journal of Haematology*. 2009; 145(3):369–372. [PubMed: 19344403]
52. Wheeler C, Eickhoff C, Elias A, et al. High-dose cyclophosphamide, carmustine, and etoposide with autologous transplantation in Hodgkin's disease: A prognostic model for treatment outcomes. *Biology of Blood and Marrow Transplantation*. 1997; 3(2):98–106. [PubMed: 9267670]
53. Forrest DL, Hogge DE, Nevill TJ, et al. High-dose therapy and autologous hematopoietic stem-cell transplantation does not increase the risk of second neoplasms for patients with Hodgkin's lymphoma: A comparison of conventional therapy alone versus conventional therapy followed by autologous hematopoietic stem-cell transplantation. *Journal of Clinical Oncology*. 2005; 23(31):7994–8002. [PubMed: 16204014]
54. André M, Henry-Amar M, Blaise D, et al. Treatment-related deaths and second cancer risk after autologous stem- cell transplantation for Hodgkin's disease. *Blood*. 1998; 92(6):1933–1940. [PubMed: 9731050]
55. Goodman KA, Riedel E, Serrano V, Gulati S, Moskowitz CH, Yahalom J. Long-term effects of high-dose chemotherapy and radiation for relapsed and refractory Hodgkin's lymphoma. *Journal of Clinical Oncology*. 2008; 26(32):5240–5247. [PubMed: 18809615]

Summary

The management of relapsed and refractory Hodgkin lymphoma remains a challenge, and previous studies have investigated various approaches. Here we present a systematic multimodality salvage approach including salvage chemotherapy, total lymphoid irradiation, high-dose chemotherapy and transplant. We found that excellent long-term outcomes with limited toxicities can be achieved with this approach; patients with primary refractory and extranodal disease had poorer outcomes; and complete response to salvage chemotherapy was the greatest predictor of long-term survival.

Event-Free Survival

Figure 1. Survival outcomes

a: Overall survival

b: Event-free survival

c: Disease-specific survival

Salvage Response on OS

Salvage Response on EFS

Figure 2. Response to salvage therapy

a: Overall survival by response to salvage therapy

b: Event-free survival by response to salvage therapy

c: Disease-specific survival by response to salvage therapy

Table 1

Patient and disease characteristics

Characteristic	N (%)
Median age at diagnosis	30
Range	5 to 64
Median age at transplantation [years]	32
Range	12 to 66
Sex	
Male	94 (51)
Female	92 (49)
Histology	
NS	153 (82)
MC	21 (11)
LP	5 (3)
Other	7 (4)
Stage at diagnosis	
I	8 (4)
II	67 (36)
III	67 (36)
IV	44 (24)
Stage at relapse	
I	22 (12)
II	74 (40)
III	38 (20)
IV	52 (28)
B symptoms	
At diagnosis	
No	70 (38)
Yes	116 (62)
At relapse	
No	129 (69)
Yes	57 (31)
Pruritus	
At diagnosis	
No	143 (77)
Yes	43 (23)
At relapse	
No	154 (83)
Yes	32 (17)

Characteristic	N (%)
Bulky disease	
At diagnosis	
No	67 (36)
Yes	84 (45)
Unknown	35 (19)
At relapse	
No	101 (54)
Yes	62 (33)
Unknown	23 (12)
Extranodal disease	
At diagnosis	
No	122 (66)
Yes	64 (34)
At relapse	
No	138 (74)
Yes	48 (26)
Functional imaging	
After initial treatment	
Gallium scan	52 (28)
PET scan	52 (28)
Neither	82 (44)
Both	0 (0)
After standard dose salvage chemotherapy	
Gallium scan	55 (29.5)
PET scan	60 (32)
Neither	70 (38)
Both	1 (0.5)
Response to initial therapy	
CR	87 (47)
PR	41 (22)
SD	7 (4)
POD	50 (27)
Response to salvage therapy	
CR	102 (55)
PR	49 (26)
SD	9 (5)
POD	11 (6)
Unknown	15 (8)
Three-factor risk model	
1	114 (61)

Characteristic	N (%)
2	54 (29)
3	18 (10)
Interval in remission	
<12 months	149 (80)
12 months	37 (20)
Primary refractory disease	
No	88 (47)
Yes	98 (53)
Involved field radiation boost	
No	12 (6)
Yes	174 (94)
Type of transplantation	
ABMT	70 (37.5)
ASCT	111 (60)
Double ASCT	5 (2.5)
Era of transplantation	
1985 to 1998 (Introduction of risk-stratified transplantation)	90 (48)
1998 to 2008	96 (52)

* Abbreviations: NS, nodular sclerosing; MC, mantle cell; LP, lymphocyte predominant; CR, complete response; PR, partial response; SD, stable disease; POD, progression of disease; ABMT, autologous bone marrow transplantation; ASCT, autologous stem-cell transplantation

Table 2

Univariate and multivariate analysis for association with overall survival

Variable	Univariate analysis Hazard ratio (95% CI)	p-value	Multivariate analysis Hazard ratio (95% CI)	p-value
Initial Stage (late vs early)	1.14 (0.68 to 1.93)	0.62		
Extranodal disease at diagnosis	1.01 (0.61 to 1.67)	0.98		
Initial B-symptoms	1.02 (0.60 to 1.72)	0.95		
Bulky disease at diagnosis (>5cm) [†]	1.89 (1.01 to 3.53)	0.047		
CR to initial therapy	0.59 (0.36 to 0.98)	0.04		
Three-factor risk model (risk category 2 vs 1)	1.13 (0.65 to 1.96)	0.67		
Three-factor risk model (risk category 3 vs 1)	2.24 (1.13 to 4.46)	0.02		
Relapsed vs refractory	0.60 (0.36 to 1.00)	0.05		
Stage at recurrence (late vs early)	1.33 (0.81 to 2.18)	0.26		
Extranodal disease at relapse	1.44 (0.85 to 2.44)	0.17		
B-symptoms at relapse	1.30 (0.79 to 2.14)	0.31		
Bulky disease at relapse (>5cm) [‡]	1.05 (0.60 to 1.81)	0.88		
CR to standard dose salvage chemotherapy [*]	0.33 (0.19 to 0.57)	<0.0001	0.33 (0.19 to 0.57)	<0.0001
ASCT post 1998	0.52 (0.30 to 0.91)	0.02		
ASCT post 1995	0.53 (0.32 to 0.89)	0.02		

* Abbreviations: CR, complete response; ASCT, autologous stem-cell transplantation

[†] These categories contained missing values (see Table 1).

[‡] These categories were excluded from the multivariable analysis due to substantial missing values (see Table 1). Of the categories “Three-factor risk model, CR to initial therapy and relapsed vs refractory disease” only relapsed vs refractory disease was evaluated to reduce multi-collinearity due to the high correlation of the three variables; similarly, of the two transplant eras, only ASCT post 1995 was selected for multivariable analysis.

Table 3

Univariate and multivariate analysis for association with event-free survival

Variable	Univariate analysis Hazard ratio (95% CI)	p-value	Multivariate analysis Hazard ratio (95% CI)	p-value
Initial Stage (late vs early)	1.49 (0.91 to 2.43)	0.11		
Extranodal disease at diagnosis	1.07 (0.67 to 1.71)	0.78		
Initial B-symptoms	1.06 (0.66 to 1.71)	0.81		
Bulky disease at diagnosis (>5cm) [†]	1.67 (0.95 to 2.93)	0.07		
CR to initial therapy	0.52 (0.32 to 0.83)	0.006		
Three-factor risk model (risk category 2 vs 1)	1.44 (0.88 to 2.38)	0.15		
Three-factor risk model (risk category 3 vs 1)	2.64 (1.37 to 5.07)	0.004		
Relapsed vs refractory	0.53 (0.33 to 0.85)	0.007	0.59 (0.36 to 0.96)	0.03
Stage at recurrence (late vs early)	1.63 (1.03 to 2.57)	0.04		
Extranodal disease at relapse	1.60 (0.99 to 2.58)	0.053		
B-symptoms at relapse	1.56 (0.98 to 2.47)	0.059		
Bulky disease at relapse (>5cm) [‡]	1.27 (0.77 to 2.08)	0.34		
CR to standard dose salvage chemotherapy [*]	0.34 (0.21 to 0.56)	<0.0001	0.37 (0.23 to 0.61)	<0.0001
ASCT post 1998	0.62 (0.38 to 1.00)	0.05		
ASCT post 1995	0.60 (0.37 to 0.96)	0.03		

* Abbreviations: CR, complete response; ASCT, autologous stem-cell transplantation

[†] These categories contained missing values (see Table 1)

[‡] These categories were excluded from the multivariable analysis due to substantial missing values (see Table 1). Of the categories “Three-factor risk model, CR to initial therapy and relapsed vs refractory disease” only relapsed vs refractory disease was evaluated to reduce multi-collinearity due to the high correlation of the three variables; similarly, of the two transplant eras, only ASCT era post 1995 was selected for multivariable analysis.

Table 4

Univariate and multivariate analysis for association with disease-specific survival

Variable	Univariate analysis Hazard ratio (95% CI)	p-value	Multivariate analysis Hazard ratio (95% CI)	p-value
Initial Stage (late vs early)	1.27 (0.65 to 2.50)	0.49		
Extranodal disease at diagnosis	1.22 (0.64 to 2.31)	0.55		
Initial B-symptoms	1.30 (0.65 to 2.61)	0.46		
Bulky disease at diagnosis (>5cm) [†]	2.43 (1.08 to 5.47)	0.03		
CR to initial therapy	0.31 (0.15 to 0.67)	0.003		
Three-factor risk model (risk category 2 vs 1)	0.85 (0.38 to 1.86)	0.68		
Three-factor risk model (risk category 3 vs 1)	3.48 (1.66 to 7.32)	0.001		
Relapsed vs refractory	0.36 (0.17 to 0.75)	0.004	0.38 (0.18 to 0.79)	0.009
Stage at recurrence (late vs early)	1.11 (0.59 to 2.10)	0.74		
Extranodal disease at relapse	2.12 (1.12 to 4.00)	0.02	1.97 (1.04 to 3.75)	0.04
B-symptoms at relapse	1.25 (0.65 to 2.40)	0.51		
Bulky disease at relapse (>5cm) [‡]	1.10 (0.56 to 2.18)	0.78		
CR to standard dose salvage chemotherapy [*]	0.49 (0.25 to 0.94)	0.04		
ASCT post 1998	0.65 (0.33 to 1.28)	0.21		
ASCT post 1995	0.65 (0.34 to 1.24)	0.19		

* Abbreviations: CR, complete response; ASCT, autologous stem-cell transplantation

[†] These categories contained missing values (see Table 1).

[‡] These categories were excluded from the multivariable analysis due to substantial missing values (see Table 1). Of the categories “Three-factor risk model, CR to initial therapy and relapsed vs refractory disease” only relapsed vs refractory disease was evaluated to reduce multi-collinearity due to the high correlation of the three variables; similarly, of the two transplant eras, only ASCT era post 1995 was selected for multivariable analysis.