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Patterns of Relapse After Salvage Autologous Stem Cell Transplant for Hodgkin's Lymphoma: Should Sites of Relapse Relative to Initially Involved Sites Be Used to Guide Indications for Peri-Transplant Radiation Therapy

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Abstract

Purpose: We aimed to assess patterns of relapse in patients undergoing salvage autologous stem cell transplant (ASCT) for relapsed Hodgkin lymphoma in the modern era with the hypothesis that patients who suffer a relapse at initially involved sites are at increased risks of relapse post-ASCT that may help guide the application of peri-transplant radiation therapy.

Methods and Materials: A retrospective review was conducted of 38 patients undergoing ASCT between 2002 and 2017 for relapsed or refractory Hodgkin lymphoma. The site of relapse at the time of ASCT and subsequent relapses were compared with sites of the initial involvement at the time of diagnosis using follow-up imaging (most commonly positron emission computed tomography). Relapse and overall survival rates were calculated from the date of ASCT using the Kaplan-Meier method with a multivariate analysis, completed using a Cox multivariate analysis.

Results: The median follow-up time was 38 months (interquartile range, 18–66 months). Twenty-two patients (58%) suffered a relapse after ASCT at a median time to relapse of 9.1 months (interquartile range, 2.9–12.3 months) with a 5-year risk of relapse of 58% (95% confidence interval [CI], 41%–75%). On univariate analysis, relapse at an initially involved site was significant for higher rates of relapse at 71% at 5-years (95% CI, 52%–90%) compared with relapse at initially uninvolved sites at 30% (95% CI, 2%–58%; $P = .05$). The relapse rate was also significantly higher in patients age <30 years at the time of diagnosis at 80% (95% CI, 59%–100%) compared with 40% (95% CI, 18%–62%) at 5 years in patients aged >30 years ($P < .01$). On multivariate analysis, relapse at initially involved sites was significant for higher rates of relapse (hazard ratio: 8.3; 95% CI, 1.2–57.4; $P = .03$).

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Supplementary Data

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Conclusions: Relapses at initially involved sites may potentially increase the risk of relapse after ASCT. Additional studies are needed to clarify whether this should be used as an additional factor to guide recommendations for peri-transplant radiation therapy.

Introduction

With the evolution of therapy in classic Hodgkin lymphoma (HL) from wide-field radiation therapy (RT) alone to combined modality therapy to increasingly chemotherapy alone, the treatment of HL is one of the great success stories of modern medicine with generally high cure rates, leading to modern trials that examine the role of de-intensification of therapy to reduce the late effects of treatment.¹ However, multiple recent trials have highlighted that the omission of RT comes at a cost (albeit small) of increases in progression-free survival, even in favorable subsets of patients with interim complete positron emission tomography (PET)/computed tomography (CT) response.^{2,3} Because chemotherapy alone strategies are increasingly adopted on a national level, the importance of successful salvage therapy for the subset of patients who suffer progression after upfront therapy becomes of paramount importance.⁴

Historically, treatment with salvage chemotherapy or autologous stem cell transplant (ASCT) salvages approximately 50% of patients with relapsed HL. These numbers are expected to increase with the addition of novel therapies, such as C30-targeted antibody-drug conjugate therapy with brentuximab vedotin and immunotherapies such as nivolumab.⁵⁻⁷ RT is increasingly omitted from upfront treatment strategies; therefore, RT as an important adjunct to these novel strategies in the treatment armamentarium for relapsed or refractory HL, especially considering RT's role in salvage therapy, may be increasingly important in relapsed patients who have not received RT as part of upfront therapy in overcoming chemotherapy resistance.

To this end, consensus guidelines have been published by the International Lymphoma Radiation Oncology Group to better guide the potential application of RT in relapsed or refractory HL.⁸ These guidelines have focused on the classic indications for RT, such as bulky disease, incomplete response by PET/CT after salvage chemotherapy, and other situations critical for local control (eg, spinal cord, vascular, or airway compression). However, we propose that an additional indication for peri-transplant RT might be relapse in a previously involved but unirradiated site because this might be a manifestation of chemotherapy resistant clonogens (Fig. 1). These resistant populations may be overcome by maximizing local control with the addition of peri-transplant RT.

Thus, we aimed to review patterns of relapse after salvage chemotherapy and ASCT and focused on patterns of relapse with the hypothesis that a relapse at a previously involved site might be a marker for increased risk of relapse after salvage therapy. The null hypothesis was that relapse after upfront chemotherapy at initially involved sites does not predict for increased risk of post-ASCT relapse.

Methods and Materials

After approval by the institutional review board, patients undergoing salvage for relapsed or refractory classical HL between 2002 and 2017 were retrospectively reviewed. Patients were identified through a prospectively maintained institutional transplant database. All records of patients treated at our institution with ASCT between 2002 to 2017 were maintained in this database prospectively. Patients were excluded if they had incomplete records ($n = 87$). A large number of patients were excluded owing to changes in electronic medical record—limiting records for patients in the bone marrow transplant database treated before 2006.

One patient did not have complete records to ascertain the exact sites of relapse and initial involvement and was excluded from the analyses of patterns of relapse by sites of involvement. In addition, 3 patients who received peri-transplant RT were excluded from the analysis owing to the lack of generalizability associated with their inclusion and likely effect of RT on recurrence post-ASCT. Site of relapse before salvage therapy and ASCT and subsequent relapse after ASCT were compared with sites of initial involvement at the time of diagnosis using follow-up imaging (most commonly PET/CT).

Response to therapy was graded based on radiologist interpretation of the PET/CT responses. Responses included complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD) and were based on radiologist interpretation of the images. Patients were considered to have relapsed if the initial tumor response returned after a period of at least 90 days. Patients were considered to have refractory disease if the tumor burden was stable, progressed after treatment, or recurred within 90 days of initial therapy.⁹ Patients were considered to have bulky disease if tumors were more than one-third of the mediastinal thoracic ratio or 10 cm.

Relapse and overall survival rates were calculated from the date of ASCT to the date of event or last follow-up using the Kaplan-Meier method, with comparisons between the groups completed using the log-rank method. A multivariate analysis was completed using a Cox multivariate analysis with forced entry methodology of the following observed covariates, including relapsed versus refractory, stage at the time of diagnosis, stage at the time of relapse, presence of B symptoms at the time of the initial diagnosis, upfront RT received, PET/CT response to salvage chemotherapy, age at the time of diagnosis, age at the time of relapse, relapse within 12 months of initial disease remission, presence of extranodal disease at the time of relapse, and relapse at an initially involved site. Owing to a small number of events with potential covariates, sensitivity analyses were performed using a parsimonious Cox multivariate model formed using forward selection of only covariates that were significant on univariate analysis. The statistics were performed using IBM SPSS, version 24 (IBM Corporation, Armonk, NY). A $P < .05$ was considered significant for all analyses.

Results

Patient characteristics

A total of 38 patients who had received ASCT after failing upfront therapy were included in the study. Patient and disease characteristics are summarized in Table 1. The median age at the time of ASCT was 33.5 years, and the stage at the time of relapse was I to II in 45% of patients. With regard to upfront therapy, 79% of patients received chemotherapy alone, with the majority treated with adriamycin, bleomycin, vinblastine, and dacarbazine at a median of 6 cycles with no initial RT included. Eight patients (21%) received RT as part of their upfront treatment. Two patients (5%) received brentuximab before ASCT relapse, and 10 patients (26%) received brentuximab after ASCT in varying sequences of their salvage therapies.

Radiation records were incomplete for patients regarding upfront RT received. Of the 8 patients who received upfront radiation, 2 patients received mantle radiation and 1 patient received involved field RT to the neck and mediastinum with a total of 18 fractions completed. Another patient had 9 Gy delivered in 3 fractions before initial chemotherapy, followed by 28.8 Gy delivered to the mediastinum in an unrecorded number of fractions. Details regarding upfront RT were unknown for the remaining 4 patients.

Clinical outcomes

The median follow-up time, calculated as the median of the follow-up time, was 38 months for all patients (interquartile range [IQR], 18–66 months) and 47 months for surviving patients (IQR, 26–83 months). A total of 10 deaths were reported. Twenty-two patients (58%) suffered a relapse of disease after ASCT, with a median time to relapse of 9.1 months (IQR, 2.9–12.3 months) and 5-year risk of relapse of 58% (95% CI, 41%–75%). Overall, these 22 patients with a post-ASCT relapse represent 42% of the total population studied who had documented sites of initial involvement. Of those 22 patients, 16 patients (73%) relapsed after ASCT at sites that were initially involved at the time of the original diagnosis. Fourteen of those 16 patients (88%) had a pre-ASCT relapse at sites of involvement that also matched the initial sites of involvement at the time of diagnosis. Only 1 patient had RT as part of upfront therapy. No patients experienced any peri-transplant mortality within 90 days of the transplant. A flowsheet graphical representation was included to outline each patient's course of therapy, including upfront chemotherapy and salvage chemotherapy regimens, postsalvage chemotherapy response, pre-ASCT preparative regimen, and post-ASCT relapse (Fig. 2).

A univariate analysis was performed to assess for a correlation between different patient characteristics and outcomes. No difference was found in the post-ASCT relapse rates when comparing relapsed versus refractory HL, stage at the time of diagnosis and relapse, presence versus absence of B symptoms at the time of diagnosis, initial or peri-transplant RT, response to salvage chemotherapy, presence of mediastinal versus other sites of initial disease, or age at the time of relapse. However, pre-ASCT relapse at an initially involved site of disease was significant for higher rates post-ASCT relapse at 71% (95% CI, 52%–90%) at 5-years compared with 30% (95% CI, 2%–58%; $P = .05$) in patients whose initial relapse

was at a previously uninvolved site (Fig. 3A). In addition, relapse rates were significantly higher in patients aged <30 years at the time of diagnosis at 80% (95% CI, 59%–100%) compared with 40% (95% CI, 18%–62%) at 5-years in patients aged >30 years ($P < .01$).

A forced-entry method multivariate analysis was performed with the intention of controlling for confounding variables as outlined and demonstrated that pre-ASCT relapse at initially involved sites of disease was significant for higher rates of post-ASCT relapse compared with pre-ASCT relapse at initially uninvolved sites (hazard ratio [HR]: 8.3; 95% CI, 1.2–57.4; $P = .03$; Fig. 3B). Additional significant variables included the presence of B symptoms at the time of initial diagnosis (HR: 8.3; 95% CI, 1.3–53.4; $P = .03$) and age at the time of initial diagnosis (HR: 0.14; 95% CI, 0.03–0.60; $P < .01$).

Other covariates tested, including relapsed versus refractory, stage at the time of diagnosis, stage at the time of relapse, upfront RT as part of the initial management, PET/CT response to salvage chemotherapy, age at the time of relapse, relapse within 12 months of initial disease remission, and extranodal disease at the time of relapse, showed no significant correlation with post-ASCT relapse rates (Table 2). Owing to the small sample size with a small number of events relative to potential covariates, a sensitivity analysis was performed using forward conditional selection and confirmed the impact of age at the time of initial diagnosis as the only significant predictor for relapse-free survival (Appendix).

The 5-year overall survival rate was 71% (95% CI, 53%–89%) with a total of 10 deaths. The univariate analysis showed no difference when comparing relapsed versus refractory HL, stage at the time of diagnosis and relapse, presence versus absence of B symptoms at the time of diagnosis, upfront RT, or age at the time of diagnosis or relapse, and mediastinal versus other sites of initial involvement. For relapse at the initially involved site compared with initially uninvolved site, the overall survival rate was 100% (95% CI, 100%–100%) versus 58% (95% CI, 34%–82%; $P = .02$) at 5 years. Response to salvage chemotherapy predicted for 5-year overall survival was 43% (95% CI, 4%–82%) for patients who achieved CR in response to salvage chemotherapy versus 82% (95% CI, 63%–100%) in all other groups (ie, PR, PD, SD; $P = .02$). This was confirmed only for response to salvage chemotherapy on multivariate analysis, defined as PET/CT response to salvage chemotherapy (HR: 6.2; 95% CI, 1.5–25.6; $P = .01$; Appendix).

Discussion

The role of peri-transplant RT remains controversial in the management of relapsed or refractory HL, and recent guidelines focus on classic indications for RT including bulk, incomplete response by PET/CT, and situations critical for local control (eg, spinal cord, vascular, or airway compression).⁸ Herein, we examined patterns of relapse after ASCT for relapsed or refractory HL in a population predominantly managed with chemotherapy alone for upfront therapy (79% chemotherapy alone) and without peri-transplant RT at the time of salvage ASCT, which is reflective of the national trends in HL management toward chemotherapy-alone strategies.⁴

Our results highlight that patients who suffer a pre-ASCT relapse at initially involved sites of the disease are at a significantly higher risk of post-ASCT relapse compared with patients who relapse pre-ASCT at initially uninvolved sites. This raises the question whether a relapse at an initially involved site from the time of diagnosis might also be used as an indication for peri-transplant RT in relapse or refractory HL, especially in the era of chemotherapy alone for upfront treatment of HL.

With no prospective studies to date to guide the application of peri-transplant RT and mixed results in retrospective studies, the role of peri-transplant RT has remained controversial.^{10–12} An older study from the mid-1990s, when RT was part of the standard upfront therapy (55% of included patients received upfront RT as part of combined modality therapy), highlighted the increased risk of relapse in sites of previous involvement, which was abrogated by the addition of peri-transplant RT.¹³ In addition, more recent multi-institutional data have shown that the omission of RT as part of upfront therapy was associated with decreased salvage rates with ASCT.¹⁰ Combined, these results form the underlying hypothesis for the present study: With the decreased use of RT in upfront therapy (21% of our included patients received RT as a part of upfront, combined, modality therapy), the pattern of relapse previously noted by Mundt et al might be magnified.¹³ Our null hypothesis was rejected, as shown with a HR for relapse of 8.3 on multivariate analysis for patients who suffer a pre-ASCT relapse at a site of involvement at the time of diagnosis. This suggests that patients who suffer a pre-ASCT relapse at initially involved sites of disease are at a significantly higher risk of post-ASCT relapse compared with patients who relapse pre-ASCT at initially uninvolved sites. However, of note, although this observed difference in our data set was of significance for relapse-free survival, this observation could not be confirmed on multivariate analysis for overall survival; thus, additional studies are warranted to better confirm or refute this finding.

Owing to a low overall number of patients who received peri-transplant RT in our bone marrow transplant database, these patients were excluded from the analysis, and as such, the presented study cannot speak to the effect of peri-transplant RT to alter this risk of relapse. However, prior studies have shown that the risk of relapse in a site of disease that receives peri-transplant RT is <10% to 20%, which suggests that peri-transplant RT can be a powerful local-control therapy in relapsed or refractory HL.^{10,14,15} In addition, other studies have demonstrated a propensity for patients with HL to relapse at initially involved sites after high-dose chemotherapy and ASCT, but early stage HL tends to recur in initial sites only compared with late stage HL, which recurs in multiple as well as extranodal locations, including initial sites.¹⁶ An additional potential barrier to the application of peri-transplant RT aside from well-defined indications is the concern of added toxicity with ASCT. Prior reports have suggested high rates of toxicity with peri-transplant RT,¹⁷ but modern series have shown that, when using modern RT volumes and techniques, the risks of severe toxicity are low.¹⁰

The present study has inherent limitations of retrospective design, but patients were identified through a prospectively maintained institutional transplant database, which likely reduced any perceived selection bias in case selection. Low numbers and events decreased the power of the study to detect differences in outcomes (eg, we did not identify a difference

in relapse by previous factors identified to impact relapse after ASCT, such incomplete response to salvage chemotherapy or B-symptoms).^{10–12,15} Moreover, our data demonstrated that a CR to salvage chemotherapy predicted for decreased 5-year overall survival compared with patients with an incomplete response, which is contrary to the results of previously published reports.^{18–20} This may relate to the small sample size and confounding because this difference was not reflected in the analysis of relapse-free survival, which was as expected numerically higher in the CR group.

In addition, this difference may speak to another limitation to the present study. Response to initial, salvage, and ASCT treatments were graded based on PET/CT response rather than Deauville score because many of these patients were treated before the existence of this grading system. PET/CT images were not universally available to us to apply the scoring system retrospectively because of changes in imaging software over the period of time examined. Therefore, we used radiologist interpretation of CR, PR, PD, or SD as responses to these therapies, which may have led to a misclassification of response.

Moreover, because of the small numbers and retrospective design, the presented analysis does not take into account the additional impact of novel systemic therapies, such as brentuximab vedotin, on patterns of relapse owing to the inconsistent patterns of incorporation for the 12 patients who received brentuximab. As stated previously, an additional limitation of the present study is the small number of events relative to potential covariates; therefore, sensitivity analyses were performed using a parsimonious Cox multivariate model formed using forward selection of only covariates that were significant on univariate analysis. Combined, despite these limitations, the present analysis generates a hypothesis that sites of disease relapse after initial therapy can potentially guide the application of peri-transplant RT.

Conclusions

As demonstrated herein, a relapse at initially involved sites correlates with an increased risk of relapse after ASCT. Further studies are needed to clarify whether this should be used as an additional factor to guide recommendations for peri-transplant RT as an adjunct to classic indications in the modern era when chemotherapy alone is increasingly incorporated as upfront therapy over combined modality therapy, worthy of continued validation in larger cohorts, and incorporation of additional strategies to personalize care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

Case example of multiply relapsed Hodgkin lymphoma. (A) A 56-year-old patient with initial diagnosis of stage IIB classic Hodgkin's lymphoma who achieved complete response (Deauville score: 2) after initial therapy of 4 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine without irradiation. (B) Fifteen months after completion of initial therapy, the patient relapsed with involvement at the right hilum and mediastinal stations 3a and 7. The patient was treated with an additional 8 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine without irradiation. (C) Subsequently, after 21 months, the patient developed a relapse in the mediastinal level 7 and right hilar lymph nodes, and received salvage treatment with ifosfamide, carboplatin, and etoposide, and autologous stem cell transplant with cyclophosphamide, BCNU, and VP-16 conditioning. (D) Repeat positron emission tomography/computed tomography scan post-transplant on day 80 showed a Deauville score of 4 response.

Fig. 2.

Treatment schema: Graphical representation of all patient treatments from the time of initial diagnosis, demonstrating the range of initial and salvage chemotherapy regimens, the response to these regimens, and preparative regimens before autologous stem cell transplantation. The postautologous stem cell transplantation relapse status is represented in the final panel.

*Of the 36 patients who had ABVD, 25 patients had 6 cycles, 3 patients had 8 cycles, 3 patients had 4 cycles, 1 patient had 3 cycles, and 1 patient had 1 cycle, 3 patients were unknown.

Fig. 3.
 (A) Univariate survival estimate and (B) multivariate analyses of relapse-free survival after autologous stem cell transplant, comparing a patient with preautologous stem cell transplant relapse at the initially involved versus uninvolved site from the time of the initial diagnosis.

Table 1**Baseline characteristics**

Patient characteristic, n (%)	
Sex	
Male	24 (63)
Female	14 (37)
Median age at time of diagnosis, years	30
Median age at time of ASCT, years	33.5
Stage at time of diagnosis	
I-II	17 (45)
III-IV	21 (55)
Relapsed	22 (58)
Refractory	16 (42)
Bulky at time of diagnosis	
Yes	8 (21)
No	28 (74)
Unknown	2 (5)
B symptoms	
Yes	24 (63)
No	14 (37)
ECOG performance status score	
0	14 (37)
1	15 (39)
2	2(5)
Unknown	7 (18)
Extranodal involvement *	
Yes	11 (29)
No	22 (58)
Unknown	5 (13)
Extranodal involvement at time of relapse	
Yes	10 (26)
No	22 (58)
Unknown	6 (16)
Initial radiation therapy	
Yes	8 (21)
No	30 (79)
Stage at time of relapse	
I-II	15 (39)
III-IV	17 (45)
Unknown	6 (16)
Median Remission Duration after First Line Therapy (days)	131
Relapse within 12 months of initial remission	

Patient characteristic, n (%)	
Yes	26 (68)
No	12 (32)
Response to salvage chemotherapy (PET/CT)	
Progression	5 (13)
Stable disease	1 (3)
Partial response	15 (39)
Complete response	15 (39)
Unknown	2 (5)

Abbreviations: ASCT = autologous stem cell transplantation; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; PET = positron emission tomography.

* Sites of extranodal involvement included the following: 1) spleen; 2) diffuse pulmonary, hepatic, splenic, and focal vertebral; 3) borderline malignant pleural effusions and bony lesions in the right posterior iliac spine/sacrum; 4) lumbar/sacral spine involvement; 5) lung parenchymal disease; 6) right lower lobe lung parenchymal and bone marrow focal involvement; 7) bony lytic lesions; 8) lung parenchymal; 9) anterior mediastinum/parenchymal involvement; and 10) unknown (n = 2).

Table 2

MVA for relapse after autologous stem cell transplant

Patient characteristics	HR (95% CI)	P-value
Relapsed vs refractory	3.73 (0.69–20.24)	.13
Stage at time of diagnosis	1.23 (0.25–5.98)	.81
Stage at time of relapse	0.48 (0.08–3.02)	.43
Presence of B Symptoms at time of initial diagnosis	8.28 (1.28–53.41)	.03
Received upfront radiation therapy	0.54 (0.10–2.85)	.46
PET/CT response to salvage chemotherapy	0.44 (0.13–1.54)	.20
Age at time of diagnosis	0.14 (0.03–0.60)	<.01
Age at time of relapse	1.23 (0.36–4.22)	.74
Relapse at initially involved site (pre-ASCT)	8.30 (1.20–57.42)	.03
Relapse within 12 mo of initial disease remission	2.45 (0.43–14.03)	.13
Extranodal disease at time of relapse	1.50 (0.32–6.89)	.31

Abbreviations: ASCT = autologous stem cell transplantation; CI = confidence interval; CT = computed tomography; HR = hazard ratio; PET = positron emission tomography.

Enter method multivariate analysis with all covariates included.