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Consolidative radiotherapy following autologous stem cell transplant for relapsed or refractory diffuse large B-cell lymphoma.

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Abstract

Purpose: To evaluate the role of consolidative radiotherapy in patients undergoing high dose chemotherapy and autologous stem cell transplant for relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Methods and Materials: We reviewed the medical records of 72 consecutive patients who underwent autologous stem cell transplant for relapsed or refractory DLBCL at XXXX from 2006 to 2014. Pre-transplant conditioning consisted of high-dose chemotherapy and total body irradiation. Thirteen patients received post-transplant consolidative radiotherapy at the discretion of the consulted radiation oncologist.

Results: Consolidative radiotherapy was associated with a significantly improved 2-year locoregional control (LRC) (92% vs 68%, $p=0.04$) although there was no difference in either the 2-year progression-free survival (PFS) (69% vs 54%, $p=0.25$) or overall survival (OS) (85% vs 59%, $p=0.44$). Analysis of the subgroup of 19 patients who had persistent residual masses ≥ 2 cm on post-transplant imaging demonstrated a significant improvement in the LRC (100% vs 36%, $p<0.01$) as well as the PFS (88% vs 27%, $p=0.01$) and OS (100% vs 45%, $p=0.02$) with consolidative radiotherapy.

Conclusions: The use of consolidative radiotherapy following high-dose chemotherapy and autologous stem cell transplantation for the treatment of relapsed or refractory DLBCL appears to significantly improve LRC. For patients with masses ≥ 2 cm following transplant there was also an improved 2-year PFS and OS. Prospective trials are needed to further identify the patients who would derive the most benefit from consolidative radiotherapy in the transplant setting.

Summary

Patients with relapsed or refractory diffuse large B-cell lymphoma undergoing autologous bone marrow transplant benefited from consolidative IFRT. All patients who underwent consolidative IFRT had an improved locoregional control. Additionally, patients with enlarged lymph

adenopathy had an improved locoregional control, disease free survival, and overall survival evaluated at two years.

Introduction

Diffuse large B-cell lymphoma (DLBCL) accounts for 40% of all newly diagnosed cases of non-Hodgkin's lymphoma (NHL).¹ Conventional combination chemotherapy can induce a complete response (CR) in about 60% of patients. However, some patients present with primary refractory disease and, among patients who achieve an initial CR, a significant proportion may relapse. After the conclusion of the PARMA Trial, high-dose chemotherapy (HDC) in combination with autologous stem cell transplant (ASCT) became the standard salvage approach for treatment of relapsed or refractory DLBCL.² Unfortunately, only 40 to 50% of patients with chemotherapy sensitive relapse and 30% of those with primary refractory disease will achieve long-term progression-free survival following ASCT. The patterns of failure of the patients who recur despite HDC-ASCT are largely within the sites of previous disease involvement.^{3,4} This fact has generated increased interest in the use of consolidative involved-field radiotherapy (IFRT) with the hopes of improving post-ASCT outcomes.^{2,4-6}

There have been no high-quality prospective randomized trials that have directly addressed the utility of consolidative IFRT. As a result, the benefit of radiotherapy in the transplant setting is often extrapolated from single institutional retrospective series. Review of this data, however, demonstrates conflicting information regarding the use of consolidative IFRT and its role in patients undergoing ASCT for relapsed or refractory disease.

We sought to examine the clinical efficacy of consolidative IFRT in a group of patients treated with ASCT at our institution for relapsed or refractory DLBCL. Here, we report the results of a retrospective analysis of 72 patients who had undergone HDC and ASCT following a single institutional protocol at the University of Minnesota (UMN).

Methods and Materials

Patients

We reviewed the medical records of 72 consecutive patients who underwent high-dose chemotherapy and autologous stem cell transplantation for relapsed or refractory DLBCL (43 male/29 female) at XXXX on a single institutional protocol between 2006 and 2014. This institutional protocol provided stringent inclusion criteria for patients to undergo ASCT for relapsed or refractory DLBCL including age <75, Karnofsky performance score (KPS) >80%, and no serious organ dysfunction. Patients with primary refractory disease could be considered for ASCT if they had high risk features including stage IV disease at diagnosis, LDH levels >2 times normal, or >2 extranodal sites of disease. Nine patients (12.5%) had primary refractory disease (with high risk features mentioned above), whereas 63 patients (87.5%) underwent transplant after first relapse. Many patients were in their second or greater CR (n=44). To be eligible for transplant patients had to have responded to pre-transplant conditioning to the extent that they were in remission or had responding disease as

determined by pre-transplant CT and PET scans. All patient data was prospectively collected in UMN Bone Marrow Transplantation database. These data were supplemented with details regarding radiation therapy obtained from patient medical records. The Institutional Review board at UMN approved this study.

Transplant Protocol

Transplant conditioning consisted of cyclophosphamide 60 mg/kg administered on days - 7 and -6 followed by 1320 cGy total body irradiation (TBI) delivered on days -4 through -1 in eight twice-daily fractions of 165 cGy using a parallel opposed technique.^{7,8} We reinfused previously collected peripheral blood stem cells (PBSCs) on day 0. An alternative chemotherapy-only conditioning regimen using BEAM (BCNU, etoposide, Ara-C and Melphalan) was given to patients who had received prior radiotherapy with cumulative organ dose deemed too high to safely deliver TBI (n=8).

Follow-up Protocol

All patients underwent regular restaging by CT scan at day 28 as well as 3, 6, 12, and 24 months post-transplant and by positron emission tomography (PET) at day 100. Deauville criteria were used to determine treatment response to disease. Deauville scores <4 were considered to have a complete response (CR). We re-reviewed day 28 and pre-transplant CT scans to determine the size of residual lymph nodes. Bone marrow biopsies were obtained at the time of follow-up CT scans for patients with prior marrow involvement. Patients were determined to have relapsed if new or enlarged lesions were identified on regular CT scans. Toxicities or adverse events were reported according to the NCI's Common Terminology Criteria for Adverse Events. Each category of adverse event is reported rather than simply the highest grade adverse event experienced per patient.

Consolidative Radiotherapy

Consolidative IFRT was recommended if a patient had persistent nodal masses ≥ 2 cm on day 28 CT scan, sites clinically suspicious for residual disease, or if they were felt to be at high risk of relapse. The radiation fields were selected on a case-by-case basis with the all patients undergoing CT planning with suspicious areas contoured followed by 3D conformal IFRT treatment which included adjacent nodal regions (n=12) or involved node alone (n=1). There were 19 patients with residual nodal disease ≥ 2 cm on post-transplant imaging, however, consolidative IFRT was only given to eight of these patients. Reasons for omission of the consolidative IFRT included previous radiation (n=1), comorbidities (n=4), progressive disease at the time of post-transplant imaging (n=3), and unknown reasons (n=3). An additional five patients with residual tumor volume <2 cm were treated with consolidative IFRT. Therefore, a total of 13 patients received consolidative IFRT following transplantation. The median IFRT dose was 3060 cGy (range: 3060 – 3600 cGy) completed at a median of 110 days post transplant (range: 62 –132 days).

Statistical Analysis

We defined the date of relapse for a patient as the first day that findings were observed on either clinical exam or imaging. The duration of locoregional control (LRC), progression-

free survival (PFS), and overall survival (OS) were measured from the date of transplant. For the purposes of this study, LRC was defined as disease control within the areas of involvement prior to transplantation. The distribution of LRC, PFS, and OS were estimated using the Kaplan-Meier method. The effect of consolidative IFRT on LRC, PFS, and OS were determined using log-rank Cox proportional hazards model. P-values less than 0.05 were considered to be significant.

Results

Patient characteristics are shown in Table 1. There were no significant differences between the consolidation RT group and the observation group in terms of sex, age at transplant, previous consolidative IFRT, disease status (primary refractory or relapsed), anatomic site(s) of involvement, stage at relapse, transplant conditioning regimen, or follow-up duration. Fewer patients with B symptoms received consolidative IFRT (47% vs 8%, $p<0.01$). As expected by the treatment protocol, patients who received consolidative IFRT tended to have a greater incidence of residual nodal disease ≥ 2 cm on post-transplant imaging (47% vs 19%, $p<0.01$) as well as pre-transplant imaging (62% vs 19%, $p<0.01$). Fourteen patients (19%) had prior consolidative radiotherapy, but these patients were equally likely to receive consolidative IFRT in the post-transplant setting compared to the group of patients that had not received previous radiation (15% vs 20%, $p=0.68$). The median follow-up time for the entire group was 747 days (range: 33 – 3,305 days).

Among the entire cohort, there were 31 relapses (43%) and 16 deaths (22%) within two years of transplant. Of the 31 relapses, 20 (65%) occurred at previous sites of disease, representing locoregional failures. The 2-year LRC, PFS, and OS were 72%, 57%, and 78% respectively. Of the entire series, 13 patients (18%) received consolidative IFRT to a total of 17 sites. Sites of consolidative IFRT included abdomen ($n=8$), pelvis ($n=2$), head and neck ($n=2$), mediastinum ($n=2$), and axilla ($n=2$). An association between consolidative IFRT and a significantly improved 2-year LRC (92% vs 68%, $p=0.04$) was observed, however, there was no difference in 2-year PFS (69% vs 54%, $p=0.25$) or 2-year OS (85% vs 59%, $p=0.44$). Kaplan Meier plots of the entire cohort are depicted in Figure 1.

Univariate analysis of factors affecting 2-year LRC, PFS and OS is shown in Table 2. The 2-year OS was worse among patients with B symptoms (66% vs 86% $p=0.05$) and 2 year PFS was worse for female patients (67% vs 41% $p=0.04$), but other factors were not predictive of PFS or OS.

Due to our particular interest in the utility of consolidative IFRT, we performed subgroup analysis of patients who did and did not have consolidative radiotherapy after transplant (Table 3). There was no statistically significant improvement with consolidative IFRT based on patient gender, age at transplant, date of transplant, presence of B-symptoms, previous radiotherapy, disease state (relapsed vs. primary refractory), conditioning regimen, or pre-transplant Deauville score.

Nineteen patients had enlarged nodal disease ≥ 2 cm noted on day 28 imaging. Fifteen of these patients (79%) had Deauville scores of 4 on pre-transplant PET imaging. Patients who

received consolidative IFRT had better 2-year LRC, PFS, and OS ($p<0.01$, 0.01 and 0.02 respectively). The 2-year LRC for patients who received consolidative IFRT ($n=8$) was 100% compared to 36% for those that did not receive consolidative IFRT ($n=11$, $p<0.01$). Likewise, the 2-year PFS was better (88% vs 27%, $p=0.01$) as was the 2-year OS (100% vs 45%, $p=0.02$). Kaplan-Meier plots for patients with ≥ 2 cm residual nodal disease post-transplant are depicted in Figure 2.

Stem cell transplantation with or without consolidative radiotherapy was well tolerated with acceptable toxicities. All patients developed grade 3 anemia. Other toxicities were limited to grade 1 (30 events) and grade 2 (21 events) toxicities and included diarrhea (23 events), nausea (15 events), pneumonia (4 events), pericarditis (1 event), cardiomyopathy (1 event), and arterial thrombosis (1 event). There were no treatment-associated deaths, radiation pneumonitis, or secondary malignancies observed in this patient group. There was no significant difference in the percentage of patients that had developed grade 1 or 2 toxicities between those that did or did not receive consolidative IFRT (68 vs 69%, $p=0.92$).

Discussion

In this retrospective analysis, patients selected to receive IFRT had a significant improvement in locoregional disease control among patients who underwent autologous stem cell transplant for relapsed or refractory DLBCL. Only 8% of patients who received consolidative IFRT relapsed compared to 32% in those who did not receive radiation ($p=0.04$).

There have been several other retrospective studies that addressed the use of consolidative IFRT in the peri-transplant setting (Table 4).^{3,4,6,9-14} These studies differ by subtypes of NHL included, the timing of consolidative IFRT (pre-transplant: 3,^{3,10,11} post-transplant: 6,^{4,6,9,12,13} mix: 1¹⁴), the conditioning regimen (TBI-containing: 7,^{3,6,10,11,13,14} BEAC/BEAM: 5,^{6,9,11-13} EHAP: 1¹⁴) and indications for consolidative radiotherapy. Consistent with our report, most studies found an improved outcome with consolidative IFRT^{4,6,9,10,12,13}. The results of our cohort productively adds to this data as patients were homogenous in eligibility, uniformly treated on a single treatment protocol, and consistently monitored post-transplant.

When we restricted our analysis to include only the subgroup of patients with residual nodal disease ≥ 2 cm in size seen on day 28 post-transplant imaging, we found not only a significant improvement in LRC associated with consolidative IFRT, but also in PFS and OS. The number of patients in this subset is small, but it does suggest a possible subgroup of patients who are likely to derive the greatest benefit from consolidative IFRT. The improvement observed in this particular group of patients appears to be consistent with previous reports that relapse at pre-transplant sites of disease remains the most common site of post-transplant failure. Aggressive local control via consolidative IFRT, therefore, could have an impact on transplant outcome.

Because of the potential importance of local disease control at previous sites of involvement, we re-analyzed the status of involved lymph nodes using both CT and PET data. We re-

evaluated the size of lymph nodes on the CT scans prior to transplant as well as at day 28 were re-evaluated for all 72 patients. In 19 of these patients there was at least one residual lymph node measuring ≥ 2 cm in size. The treatment protocol recommended consolidative radiotherapy in these patients, however, only 8 of the 19 patients received radiotherapy. When we reviewed the post-transplant day 100 PET/CT scans using Deauville Criteria for the 11 patients who did not receive consolidative radiotherapy, 9 were found to have a Deauville score of 4. PET reporting using Deauville Criteria was not routinely performed during the study period. In all of these cases, the radiologist interpreting the PET-CT had reported either stable disease or that the disease was responding to current treatment. This reporting style may have swayed medical oncologists away from referring patients to receive consolidative IFRT. Additionally, oncologists may have been concerned about the potential of added toxicity associated with post-transplant consolidative IFRT following TBI. Therefore, routine use of Deauville Criteria in PET scan reports of lymphomas should be recommended for standardized communication of disease status, which could have important implications for making management decisions.

A concern of using consolidative IFRT in the peri-transplant setting is the potential increase in morbidity. Depending on the site of treatment, patients are at risk of developing radiation pneumonitis, cardiomyopathy, mucositis, and secondary myelodysplastic syndromes (MDS).^{3,5,15,16} We did not observe significant radiation-related toxicities among the patients in our study. Aside from the expected grade 3 anemia from transplant, majority of the patients had only grade 1 or 2 toxicities and there was no significant difference in the frequency of toxicities between patients who did and did not receive consolidative IFRT. Many other studies have found this to be the case as well.^{9,10,14} Longer patient follow-up would be needed to assess for late effects of radiotherapy such as secondary malignancy, however, this seems to be of less concern in the DLBCL population as compared to Hodgkin lymphoma population who tend to be younger.

There is additional concern that the timing of the consolidative radiotherapy may influence toxicity. In our series, all patients who received IFRT did so after transplant, completing treatment at a median of 110 days post-transplant. We observed no added toxicity. On the contrary, *Tsang et al.* reported that eight out of ten observed transplant-related deaths were associated with pre-transplant IFRT directed at the mediastinum.¹⁶ Similarly, *Friedberg et al.* found adverse impact of pre-transplant IFRT on survival in patients undergoing transplant, which were attributed to secondary myelodysplasia or pulmonary complications.³ Fewer than 50 days between IFRT and ASCT or large radiation field size (including larger portions of the lungs) were also found to be associated with worse morbidity and mortality.^{3,5,16,17} Avoiding these hazards, *Hoppe et al.* reported that IFRT prior to HDCT in the setting of ASCT had minimal treatment-related morbidity and mortality.¹⁸ Our result suggests that if IFRT is to be considered in the transplant setting, it can be delivered after ASCT allowing for adequate recovery from the toxicity of the transplant.

The majority of patients in this series underwent a conditioning regimen which included TBI. How much the modest dose of TBI contributes to tumor control is unknown, but generally 1320 cGy would be considered an inadequate radiation dose for lymphoma. Starting in 2014 at XXXX, the ASCT preparative regimen was altered to replace TBI in the

majority of patients with BEAM (BCNU, Etoposide, Ara-C, Melphalan) chemotherapy as available data suggested it has equivalent efficacy compared to a TBI-containing regimen.¹⁹ It remains to be seen how this change will affect the LRC rate, but the change to BEAM provides an opportunity to use consolidative radiation therapy in more patients and with the possibility of delivering higher doses to achieve optimal disease control. The appropriate radiation dose in peri-transplant consolidative IFRT is not known, but in this series doses ranged from 3060 to 3600 cGy.

Conclusions

Patients with relapsed or refractory DLBCL are at high risk of relapse following autologous stem cell transplantation. The most common site of failure in these patients is at the site of disease prior to transplant reflecting poor LRC. We found that patients selected to receive consolidative radiotherapy directed at the involved sites had a significantly improved LRC. Additionally, among patients with nodal masses ≥ 2 cm on post-transplant imaging, those selected to receive IFRT had an improved PFS and OS. Further studies, ideally in the form of randomized prospective trials, are necessary to definitively determine the role of radiation in the peri-transplant setting. However, our study appears to suggest a benefit of consolidative radiation in select patient populations.

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Fig. 1.

Locoregional control rates (A) were significantly improved for patients receiving consolidative IFRT, however, there was no significant improvement in progression-free survival rates (B), and overall survival rates (C) in these patients.

Fig. 2. Locoregional control rates, progression-free survival rates (B), and overall survival rates (C) were all significantly improved for patients receiving consolidative IFRT who had post-transplant tumor sizes ≥ 2 cm.

Table 1.**Patient Characteristics**

Characteristic	Consolidative IFRT (n=13) Number (%)	Observation (n=59) Number (%)	P-value
Sex			
Male	10 (77%)	33 (56%)	0.16
Female	3 (23%)	26 (44%)	
Age at transplant (years)			
30–39	0(0%)	3(5%)	0.58
40–49	2 (15%)	10 (17%)	
50–59	7 (54%)	21 (36%)	
60–75	4 (31%)	25 (42%)	
B symptoms	1 (8%)	28 (47%)	<0.01
Previous consolidative IFRT	2(15%)	12(20%)	0.68
Disease state			
Primary refractory disease	2(15%)	7(12%)	0.73
Relapsed disease	11 (85%)	52 (88%)	
Involved sites of disease			
Head and Neck	5 (38%)	31 (53%)	0.90
Axilla	4(31%)	14(34%)	
Mediastinum	4(31%)	19(32%)	
Abdomen	9 (69%)	32 (54%)	
Pelvis	5 (38%)	25 (42%)	
Stage at time of relapse			
Stage I	1 (8%)	3(5%)	0.88
Stage II	2(15%)	6(10%)	
Stage III	4(31%)	16(27%)	
Stage IV	6(46%)	34 (58%)	
Transplant Conditioning Regimen			
TBI	11 (85%)	53 (90%)	0.59
Other	2(15%)	6(10%)	
Date of transplant			
<2010	3 (23%)	11 (19%)	0.71
2010	10 (77%)	48(81%)	
Tumor Size			
Pre-transplant tumor size ≥ 2 cm	9 (69%)	15(25%)	<0.01
Post-transplant tumor size ≥ 2 cm	8(62%)	11 (19%)	<0.01
Response to Pretransplant			
Deauville Score <4	5 (38%)	35 (59%)	0.17
Deauville Score ≥ 4	8(62%)	24(41%)	
Median length of follow up (days)	763	742	0.13

IFRT, Involved Field Radiotherapy; TBI, Total Body Irradiation

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Table 2.

Univariate Analysis of factors Associated with 2-yr LRC, PFS, and OS

Characteristic	n	LRC		PFS		OS	
	Number	number (%)	P-value	Number (%)	P-value	Number (%)	P-value
Sex							
Male	43	34(79%)	0.11	29 (67%)	0.04	31 (72%)	0.18
Female	29	18 (62%)		12 (41%)		25 (86%)	
Age at transplant (years)							
<60	43	34(79%)	0.11	27 (63%)	0.14	36 (84%)	0.15
60	29	18 (62%)		14 (48%)		20 (69%)	
Date of transplant							
<2010	14	10 (71%)	0.97	9 (64%)	0.59	11 (79%)	0.9
2010	58	42 (72%)		32 (55%)		45 (78%)	
B symptoms							
Yes	29	22 (76%)	0.70	16 (55%)	0.76	19 (66%)	0.05
No	43	30 (70%)		25 (58%)		37 (86%)	
Previous consolidative IFRT							
Yes	14	10 (71%)	0.95	8 (57%)	0.98	12 (86%)	0.49
No	58	42 (80%)		33 (57%)		44 (76%)	
Disease state							
Primary Refractory	9	6 (67%)	0.81	6 (67%)	0.56	7 (78%)	0.89
Relapsed	63	46 (73%)		35 (56%)		49 (78%)	
Conditioning regimen							
TBI-Containing	64	45 (70%)	0.33	34(53%)	0.12	48 (75%)	0.14
Other	8	7(88%)		7 (88%)		8(100%)	
Pre-transplant tumor size							
<2 cm	48	34 (71%)	0.73	27(56%)	0.83	40 (83%)	0.11
2 cm	24	18 (75%)		14 (58%)		16 (67%)	
Post-transplant Tumor Size							
<2 cm	53	39 (74%)	0.93	31 (58%)	0.96	43 (81%)	0.27
2 cm	19	13 (68%)		10 (53%)		13 (68%)	
Pre-transplant Deauville Score							
<4	40	31 (78%)	0.25	25 (63%)	0.27	32 (80%)	0.48
4	32	21 (66%)		16 (50%)		24 (75%)	
Consolidative IFRT							
Yes	13	12 (92%)	0.04	9 (69%)	0.25	11 (85%)	0.44
No	59	40 (68%)		32 (54%)		35 (59%)	
Stage at relapse							
<3	13	10 (77%)	0.92	7 (54%)	0.70	10 (77%)	0.97
3	59	43 (73%)		34 (58%)		46 (78%)	

LRC, Locoregional Control; PFS, Progression-Free Survival; OS, Overall Survival; IFRT, Involved Field Radiotherapy; TBI, Total Body Irradiation

Table 3.

Subgroup Analysis of Factors Associated with 2-yr LRC, PFS, and OS

Characteristic	n	LRC		PFS		OS	
	Number	number (%)	P-value	Number (%)	P-value	Number (%)	P-value
Sex: Male							
Consolidative IFRT	10	9(90%)	0.25	6(60%)	0.76	8(80%)	0.86
None	33	25 (76%)		23 (70%)		26 (79%)	
Sex: Female							
Consolidative IFRT	3	3(100%)	0.12	3 (100%)	0.07	3 (100%)	0.33
None	26	15 (74%)		9 (35%)		19 (73%)	
Age at transplant (years): <60							
Consolidative IFRT	9	9 (75%)	0.10	6 (67%)	0.62	8 (89%)	0.56
None	34	25(60%)		21 (62%)		28 (82%)	
Age at transplant (years): >60							
Consolidative IFRT	4	3(90%)	0.50	3 (75%)	0.31	3 (75%)	0.78
None	25	15(69%)		11 (44%)	17 (68%)		
Date of transplant: <2010							
Consolidative IFRT	10	9(100%)	0.07	6(60%)	0.57	8(80%)	0.74
None	48	33 (64%)		26 (54%)		37 (77%)	
Date of transplant: >2010							
Consolidative IFRT	3	3(100%)	0.25	3 (100%)	0.19	3 (100%)	0.33
None	11	7 (64%)		6 (55%)		8 (73%)	
B symptoms: Yes							
Consolidative IFRT	1	1(100%)	0.46	1 (100%)	0.38	1 (100%)	0.49
None	28	17(61%)		13 (46%)		18 (64%)	
B symptoms: No							
Consolidative IFRT	12	11(92%)	0.20	8 (67%)	0.58	10 (83%)	0.89
None	23	15 (65%)		11 (48%)		19 (83%)	
Previous radiotherapy: Yes							
Consolidative IFRT	2	2(100%)	0.55	2 (100%)	0.55	2 (100%)	0.55
None	12	10 (83%)		10 (83%)		10 (83%)	
Pre-transplant Deauville Score ≥ 4							
Consolidative IFRT	8	7 (88%)	0.16	5 (63%)	0.39	6 (75%)	0.86
None	24	14 (58%)		11 (46%)		18 (75%)	
Pre-transplant Deauville Score <4							
Consolidative IFRT	5	5(100%)	0.19	4(80%)	0.30	5 (100%)	0.21
None	35	26 (74%)		21 (60%)		27 (77%)	
Disease State: Primary Refractory							
Consolidative IFRT	2	2(100%)	0.31	2 (100%)	0.31	2 (100%)	0.39
None	7	4(57%)		4 (57%)		5 (71%)	
Disease State: Relapsed							
Consolidative IFRT	11	10 (91%)	0.06	7(64%)	0.42	9 (82%)	0.63

Characteristic	n	LRC		PFS		OS	
	Number	number (%)	P-value	Number (%)	P-value	Number (%)	P-value
None	52	36(69%)		28 (54%)		40(77%)	
Pre-transplant Tumor Size: ≤ 2 cm							
Consolidative IFRT	9	9(100%)	<0.01	7 (78%)	0.02	8 (89%)	0.08
None	15	5 (33%)		4 (27%)		8 (53%)	
Post transplant Tumor Size: ≤ 2 cm							
Consolidative IFRT	8	8(100%)	<0.01	7(88%)	0.01	8 (100%)	0.02
None	11	4 (36%)		3 (27%)		5 (45%)	
Stage at relapse: ≤3							
Consolidative IFRT	3	3(100%)	0.29	3 (100%)	0.11	3 (100%)	0.29
None	10	7(70%)		4(40%)		7(70%)	
Stage at relapse: >3							
Consolidative IFRT	10	10 (100%)	0.05	6(60%)	0.70	8(80%)	0.78
None	49	33(67%)		28 (57%)		38 (78%)	

LRC, Locoregional Control; PFS, Progression-Free Survival; OS, Overall Survival; IFRT, Involved Field Radiotherapy

Studies Investigating the Role of Radiotherapy in the Peritransplant Setting for Relapsed or Refractory DLBCL

Table 4.

Studies that found a significant improvement in outcome with RT																			
Author	Year	Follow-Up	Dates Patients Were Treated	Radiation Timing	Conditioning	Disease	n				LRC			DFS			OS		
							RT	NoRT	RT	NoRT	RT	P-value	RT	NoRT	P-value	RT	NoRT	P-value	RT
Mundt	1997	4 years	1990–1996	Post-Transplant	Mix, Mont DHAP or EHAP	NHL: DLBCL (58%)	7	39	100%	59%	0.04	-	-	-	-	-	-	-	-
Rapoport	1997	5 years	1988–1996	Post-Transplant	BEAC (117),TBI (18), BEAM (1)	NHL DLBCL (85%) Bulky disease included in analysis	30	28	-	-	-	35%	16%	0.04	-	-	-	-	-
Vose	2001	5 years	1989–1995	Post-Transplant	TBI (27), BEAC (27), CBV (19), Other (27)	DLBCL	69	82	-	-	-	-	-	-	-	54%	44%	0.05	-
Ochler-Janne	2008	65 months	1988–2003	Post-Transplant	CBV or BEAM	NHL (Subset analysis of DLBCL)	15	15	93%	62%	0.02	65%	51%	0.3	79%	65%	>0.05	-	-
Hoppe	2009	3 years	2000–2007	Pre-Transplant	TBI (20%)	DLBCL	47	36	94%	69%	0.006	81%	58%	0.026	-	-	-	0.22	-
Biswas	2010	3 years	1992–2005	Post-Transplant	BEAC or BEAM (mostly BEAM)	DLBCL	78	83	-	-	-	-	-	-	57%	47%	0.002	-	-
Current Study	2016	2 years	2000–20014	Post-Transplant	TBI (93%)	DLBCL	13	59	92%	68%	0.04	69%	54%	0.25	85%	59%	0.44	-	-

Studies that did not find a significant improvement in outcome with RT																			
Author	Year	Follow-Up	Dates Patients	Radiation Timing	Conditioning	Disease	n				LRC			DFS			OS		
							RT	NoRT	RT	NoRT	RT	P-value	RT	NoRT	P-value	RT	NoRT	P-value	RT
Kawalramani	2000	3 years	1993–1999	Pre-Transplant	BEAM (11), TBI (22), CBV (7), ICE (2)	DLBCL (84%), Peripheral TCell Lymphoma (14%), Anaplastic Large Cell (2%)	26	16	-	-	>0.05	-	-	-	0.22	-	-	-	0.34
Friedberg	2001	75 months	1982–1997	Pre-Transplant	TBI (+/- Cyclophosphomide)	NHL (subset analysis of DLBCL)	93	148	-	-	-	40%	40%	0.86	64 months	79 months	0.09	-	-
Wendland	2007	5 years	1990–2003	Mix: Pre (19), Post (31), Both (3)	TBI (52)	DLBCL (76%)	53	114	69%	72%	0.73	79.20%	86%	0.02	40%	47%	0.28	-	-