Involved-Field Radiotherapy Before High-Dose Therapy and Autologous Stem-Cell Rescue in Diffuse Large-Cell Lymphoma: Long-Term Disease Control and Toxicity

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ABSTRACT

Purpose
To analyze outcome, prognostic factors, and toxicities in patients with diffuse large-cell lymphoma (DLCL) who received involved-field radiotherapy (IFRT) before high-dose chemotherapy with autologous stem-cell rescue (ASCR).

Patients and Methods
Between January 1990 and August 2006, 164 patients with relapsed or refractory DLCL received IFRT at Memorial Sloan-Kettering Cancer Center (New York, NY) before high-dose chemotherapy and ASCR. IFRT was delivered to involved sites measuring more than 5 cm or to sites with residual disease more than 2 cm. Radiotherapy was administered in 1.5-Gy fractions twice daily to a total dose of 30 Gy. Progression-free survival and overall survival were calculated, and short- and long-term toxicity was assessed according to National Cancer Institute Common Toxicity Criteria (version 2.0). Median follow-up was 60 months (range, 2 to 187 months).

Results
Two- and 5-year progression-free survival was 62% and 53%; 2- and 5-year overall survival was 67% and 58%, respectively. Sixty-seven patients relapsed; only 10 patients relapsed completely within the radiotherapy field. There were seven early treatment-related mortalities and 11 secondary cancers (including four myelodysplastic syndromes), one of which occurred within the IFRT site and five after total-body irradiation.

Conclusion
Minimal treatment-related mortality and morbidity resulted from short, intensive, involved-field radiotherapy before high-dose chemotherapy and ASCR, which was incorporated into a salvage regimen for patients with relapsed/refractory DLCL. This chemoradiotherapy salvage regimen resulted in a low local relapse rate that could potentially translate into an improved total outcome.

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INTRODUCTION

Initial therapy with anthracycline-containing chemotherapy regimens cures approximately 50% of patients with diffuse large-cell lymphoma (DLCL).1,2 Those who do not respond to first-line chemotherapy or who relapse often benefit from a comprehensive second-line, high-dose therapy strategy.3 Most have not received radiation therapy (RT) with initial treatment, and integrating involved-field radiation therapy (IFRT) into their salvage program addresses the likelihood of relapse within the non-irradiated relapsed or refractory site(s).4-8 Yet, concerns regarding toxicity and doubts over the benefit from IFRT have been raised.9-11 Indeed, RT in the salvage setting has rarely been studied. Furthermore, the sparse retrospective data available are biased by patient selection, especially when IFRT is dictated by the presence of residual or originally bulky disease and the patient’s ability to tolerate additional therapy. With no clear recommendations regarding the role of IFRT in the salvage setting, the timing of IFRT administration (before or after high-dose therapy [HDT]), the RT schedule, and the dose have been poorly defined. Most reported series include a variety of indications, schedules, field sizes, and doses.7-13 For more than two decades at Memorial Sloan-Kettering Cancer Center (MSKCC; New York, NY), IFRT has been incorporated into a salvage program in all refractory and relapsed patients with DLCL who meet integration criteria. After reinduction of
standard-dose chemotherapy and stem-cell collection, IFRT is delivered in a hyperfractionated accelerated manner to reduce late toxicities while minimizing time lag to HDT and autologous stem-cell rescue (ASCR).

In this study, we report outcomes and toxicities of patients with DLCL treated at MSKCC with IFRT before HDT and ASCR during the last 17 years.

## PATIENTS AND METHODS

### Patient Characteristics

Between January 1990 and August 2006, 164 patients with DLCL received IFRT at MSKCC before HDT. The median age of the patients before salvage therapy was 46 years (range, 17 to 73 years). Patients were predominantly male (59%; n = 97) and white (92%; n = 151). During the study period, ASCR was offered to patients with transformed (low-grade lymphoma at initial diagnosis with DLCL at relapse), “high-risk” (receiving ASCR as part of up-front therapy protocol on initial diagnosis of stage IV bulky or high International Prognostic Index [IPI] score DLCL), refractory (biopsy-proven disease progression during first-line therapy or within 30 days of finishing this therapy), or relapsed lymphoma (biopsy-proven disease > 30 days after first-line therapy). Patients met basic health requirements based on the protocol at the time.

Histopathology was initially classified according to the International Working Formulation, with subsequent retrospective classification (by hematopathologist D.F.) according to the WHO system. All patients were restaged by the Ann Arbor system before salvage therapy. Age-adjusted IPI score based on Eastern Cooperative Oncology Group (ECOG) performance status of at least 2, lactate dehydrogenase (LDH) more than 200 U/L, and stage III or IV disease before starting salvage therapy (sAAIPI), was calculated for all patients with sufficient information (n = 148). Patient characteristics are listed in Table 1.

First-line therapy was influenced by the protocols at that time. One hundred thirty-three patients (81%) received CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-like chemotherapy, 29 (18%) received other doxorubicin-based regimens, and two patients were administered unknown regimens. Sixteen patients (10%) received IFRT as part of first-line therapy. All patients had chemosensitive disease after second-line chemotherapy, and 90% (n = 147) received an ifosfamide, carboplatin, etoposide (ICE)-based regimen.

IFRT, limited to no more than two anatomically involved lymph node regions,1 was administered before HDT for disease measuring at least 5 cm before salvage therapy or to sites with residual nodal masses of at least 2 cm after salvage therapy. IFRT was delivered in 1.5-Gy fractions twice daily to a total dose of 30 Gy over 10 days if followed by total-body irradiation (TBI) or to a total dose of 30 Gy over 6 days if followed by TBI, treatment era (before 1994 and 1994 to present), and stem-cell source.

Follow-Up

All patients had resting computed tomography (CT) scans 90 to 100 days after ASCR, and follow-up CT scans every 6 months for 3 years. Patients who relapsed underwent confirmatory biopsy; the sites of relapse were recorded.

### Statistical Analysis

Survival analyses were performed using the Kaplan-Meier method. Overall survival (OS) and progression-free survival (PFS) were defined as time from ASCR until last follow-up or death, and as time from ASCR until disease progression, respectively. The log-rank test was used for univariate analysis of specific characteristics, including disease status (relapse, refractory, high risk, or transformed), presalvage therapy stage (I, II v III, IV), LDH (< 200 v > 200 U/L), performance status (ECOG < 1 v ≥ 2), number of extranodal sites of disease, age (< 60 v ≥ 60 years), sAAIPI, salvage chemotherapy regimen (ICE based v non–ICE based), HDT regimen, TBI (yes v no), and stem-cell source (BM v PBSC). Factors potentially predictive of OS or PFS (P < .05) were entered into a multivariate analysis using a stepwise Cox proportional hazards regression model. Factors associated with acute treatment-related mortality, evaluated by a χ² test among the 160 patients who had at least 100 days of follow-up, included testing the use of TBI, treatment era (before 1994 and 1994 to present), and stem-cell source.
Outcomes

With a median follow-up of 5 years for surviving patients (range, 2 to 187 months), the 2- and 5-year OS was 67% and 58%, respectively (Fig 1). At last follow-up, 67 patients (41%) had relapsed. In 10 (15%), failures were outside the radiation field, and in 29 patients (43%) they occurred both inside and outside the radiation field. The site was not determined in one patient. Relapse pattern was similar regardless of TBI.

Late Toxicities

Late toxicities are also reported in Table 3. Two patients developed asymptomatic radiation fibrosis on imaging. Seven patients developed cough or mild dyspnea on exertion several months after undergoing transplantation; two received IFRT to the mediastinum. One patient who received IFRT to the para-aortic nodes developed recurrent pericarditis, and one who received IFRT to the mediastinum developed mediastinitis; both were successfully treated with steroids. Four patients developed hemorrhagic cystitis from HDT, which was treated with continuous irrigation. Symptoms resolved in one patient, resulted in grade 2 chronic renal failure (CRF) in two patients, and resulted in grade 4 CRF requiring dialysis in one patient (who received TBI with IFRT). Two patients who received TBI developed cataracts, which were treated surgically. One patient developed moderate hearing impairment (grade 3) requiring a hearing aid, thought to be a result of the HDT. Patients receiving TBI with IFRT did not have increased rates of late toxicities (Table 3).

Treatment-Related Mortality

Ten patients died as a result of treatment: eight as a result of a cardiopulmonary or infectious event (seven patients < 100 days as a result of transplant and one 238 days after transplant), and two as a result of transplant and one 238 days after transplant), and two as a result of other causes, including liver failure from hepatitis C and sepsis in an intravenous drug abuser.

Two- and 5-year PFS was 62% and 53%, respectively (Fig 1). At last follow-up, 67 patients (41%) had relapsed. In 10 (15%), failures were outside the radiation field, and in 29 patients (43%) they occurred both inside and outside the radiation field. The site was not determined in one patient. Relapse pattern was similar regardless of TBI.

Early Toxicities

Table 3 outlines acute toxicities. Three patients who received IFRT to the abdomen developed an obstruction or ileus, which was treated conservatively and resolved. Seven patients developed acute pulmonary conditions shortly after undergoing transplantation. Two patients received IFRT to the mediastinum (one also received TBI) and developed a pulmonary hemorrhage, three patients developed pulmonary infiltrates (one received IFRT to the head and neck, one received IFRT to the chest with TBI, one received IFRT to the spleen with TBI), and one patient developed right-sided Pseudomonas pneumonia after receiving IFRT to the right axilla and supraclavicular region. All patients were successfully treated with oxygen (one required intubation and ventilatory support for 2 weeks), vigorous diuresis, steroids, and broad-spectrum antibiotics, although the patient treated to the mediastinum with TBI developed long-term dyspnea on exertion. The seventh patient received IFRT to the para-aortic region and developed a cytomegalovirus (CMV) pneumonia treated with antivirals, but continued to experience mild, long-term dyspnea with exertion. Fifteen patients (13 received IFRT to the mediastinum) developed cough or mild dyspnea on exertion shortly after transplant. Three of these patients required temporary steroid treatment when symptoms persisted. Patients receiving TBI with IFRT did not have increased rates of acute toxicities (Table 3).
result of secondary malignancy. IFRT to the thorax may have contributed to the death in three patients, including two who also received TBI and one patient who had reirradiation to the mediastinum. The other five deaths were likely the result of a systemic transplant conditioning regimen, which included TBI in four instances. Table 4 describes all eight patients. Both the treatment era before 1994 (P = 0.01) and BM as the source of stem cells (P < .001) were associated with higher rates of treatment-related mortality. Although only two treatment-related deaths occurred in patients receiving IFRT without TBI, TBI was not significantly associated with an increased risk of treatment-related mortality (P = .24).

**Second Malignancy**

Eleven malignancies (excluding basal cell carcinoma of the skin) were diagnosed during follow-up. Two patients died as a result of a second malignancy, including one patient who developed myelodysplastic syndrome (MDS) that progressed to acute myelogenous leukemia (AML) and died 74 months after non-TBI HDT/ASCR. One patient developed esophageal cancer 51 months after TBI and IFRT to the mediastinum and died 6 months later. MDS was diagnosed in three patients 1 to 2 years after ASCR (two received TBI); however, two relapsed and died as a result of progression of DLCL, whereas the other underwent an allotransplant and is alive at 175 months without DLCL or MDS. Another two patients who received TBI developed Hodgkin’s lymphoma outside of the IFRT field 4 years after transplant; both were successfully treated with local therapy. Four other solid tumors developed outside the IFRT field, including a superficial bladder cancer, non–small-cell lung cancer, and two prostate cancers, all of which were successfully treated with local therapy.

**Prognostic Factors**

Univariate analyses were performed for PFS and OS on the basis of patient characteristics before salvage therapy. Significant factors are listed in Table 5. Multivariate analysis was performed, and the results are also listed in Table 5.

**DISCUSSION**

Although HDT followed by ASCR has become the standard of care in patients with relapsed or refractory DLCL,15 the implications of adding IFRT have not been fully analyzed. In this study, we evaluated a

### Table 3. Early and Late Toxicities According to National Cancer Institute Common Toxicity Criteria

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Event*</th>
<th>IFRT Only (n = 89)</th>
<th>IFRT + TBI (n = 75)</th>
<th>All (n = 164)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>Grade 1/2</td>
<td>Grade 3/4</td>
<td>Grade 1/2</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Early</td>
<td>12 13 4 4</td>
<td>3 4 3 4</td>
<td>15 9 7 4</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>15 17 0 0</td>
<td>1 1 1 1</td>
<td>16 10 1 1</td>
</tr>
<tr>
<td>Esophageal</td>
<td>Early</td>
<td>22 25 0 0</td>
<td>6 8 0 0</td>
<td>28 17 0 0</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>1 1 0 0</td>
<td>3 4 0 0</td>
<td>4 2 0 0</td>
</tr>
<tr>
<td>Lower GI</td>
<td>Early</td>
<td>34 38 3 3</td>
<td>12 16 0 0</td>
<td>46 28 3 2</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>3 3 0 0</td>
<td>1 1 0 0</td>
<td>4 2 0 0</td>
</tr>
<tr>
<td>Skin</td>
<td>Early</td>
<td>16 18 0 0</td>
<td>7 9 1 1</td>
<td>23 14 1 1</td>
</tr>
<tr>
<td></td>
<td>Late</td>
<td>0 0 0 0</td>
<td>1 1 0 0</td>
<td>1 1 0 0</td>
</tr>
<tr>
<td>Kidney†</td>
<td>Early</td>
<td>6 7 0 0</td>
<td>1 1 1 1</td>
<td>7 4 1 1</td>
</tr>
</tbody>
</table>

### Table 4. Treatment-Related CardiopulmonaryDeaths (n = 8)

<table>
<thead>
<tr>
<th>Patient Age (years)</th>
<th>IFRT Site</th>
<th>TBI</th>
<th>Stem-Cell Source</th>
<th>Toxicity</th>
<th>TTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>34</td>
<td>Mediastinum</td>
<td>Yes</td>
<td>Bone marrow</td>
<td>Acute pulmonary hemorrhage</td>
<td>30</td>
</tr>
<tr>
<td>20</td>
<td>Mediastinum</td>
<td>Yes</td>
<td>Bone marrow</td>
<td>ARDS, sepsis</td>
<td>4</td>
</tr>
<tr>
<td>27</td>
<td>Mediastinum</td>
<td>No</td>
<td>Peripheral blood</td>
<td>CHF</td>
<td>98</td>
</tr>
<tr>
<td>49</td>
<td>Supraclavicular, cervical, periaortic</td>
<td>Yes</td>
<td>Bone marrow</td>
<td>Bilateral pulmonary infiltrates</td>
<td>45</td>
</tr>
<tr>
<td>50</td>
<td>Tibia</td>
<td>Yes</td>
<td>Bone marrow</td>
<td>ARDS</td>
<td>40</td>
</tr>
<tr>
<td>73</td>
<td>Kidney</td>
<td>No</td>
<td>Peripheral blood</td>
<td>Sepsis</td>
<td>50</td>
</tr>
<tr>
<td>62</td>
<td>Hemipelvis†</td>
<td>Yes</td>
<td>Bone marrow</td>
<td>Sepsis</td>
<td>30</td>
</tr>
<tr>
<td>34</td>
<td>Axilla, periaortics, spleen</td>
<td>Yes</td>
<td>Bone marrow</td>
<td>Diffuse interstitial pneumonia</td>
<td>240</td>
</tr>
</tbody>
</table>

Abbreviations: IFRT, involved field radiotherapy; TBI, total body irradiation; TTD, days to death after transplant; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure.

*Patient developed cardiomyopathy after initial therapy that included doxorubicin and 27 Gy to the mediastinum. Subsequently received 33 Gy reirradiation to the same site (total, 60 Gy).

†Prior history of mantle-field radiotherapy as part of initial therapy.
compared with BM, and therefore quicker neutrophil recovery and therefore quicker neutrophil recovery and administered to the mediastinum or whether the patient received TBI. Additionally, 4% of patients and equally, regardless of whether IFRT was administered to the mediastinum or whether the patient received TBI. Furthermore, if we limit the analysis to patients who received PBSC transplants, IFRT seems to contribute to only 1 TRM.

More large proportion of patients who received IFRT to the mediastinum into the salvage treatment of DLCL. Our analysis indicates the addition of IFRT to the thorax before BMT for recurrent/refractory Hodgkin’s disease between 1986 and 1992, likely because of extended fields and long treatment periods. Fenske et al described five patients (18%) who received IFRT before HDT/ASCR for non-Hodgkin’s lymphoma and who had a TRM compared with one patient (2%) who did not receive IFRT in a historical group. These studies and others suggest delivering IFRT after transplant, if necessary.

However, in our program, TRM and morbidity substantially decreased since the early 1990s. The decreasing toxicity coincides with our switch in 1994 from BM-collected cells to PBSCs. This change, important in itself, was also most likely a surrogate for improvements in supportive care and in radiation planning and delivery methods. Geisler et al also reported less TRM with PBSC compared with BM (P = .001), possibly related to shorter time of engraftment with PBSC compared with BM, and therefore quicker neutrophil recovery and shorter hospital stays, or better supportive care over time. Indeed, since 1994, TRM in our salvage programs dropped from 28% to 2%; since 2000, there has not been a single TRM in 64 consecutive patients.

In our study, after evaluation by both the treating radiation oncologist and medical oncologist, IFRT likely played a role in only three acute TRMs (Table 5), whereas non-IFRT related causes (including TBI) could be implicated in the remaining patients. Furthermore, if we limit the analysis to patients who received PBSC transplants, IFRT seems to contribute to only 1 TRM.

Regarding the association of pulmonary toxicity and IFRT, a large proportion of patients who received IFRT to the mediastinum developed acute but mild grade 1 or 2 pulmonary symptoms. More significant grade 3 or 4 pulmonary toxicities occurred infrequently (4% of patients) and equally, regardless of whether IFRT was administered to the mediastinum or whether the patient received TBI. Accordingly, we continue to recommend thoracic IFRT before ASCR when patients have bulky mediastinal disease or residual disease after salvage therapy. Pulmonary toxicity is reduced with mediastinal IFRT, using post–salvage-chemotherapy disease volumes, and employing precise imaging and intensity-modulated radiation therapy (IMRT).20

Some argue that the addition of pretransplant IFRT will cause delays in transplant that can lead to relapses, and that there may be less toxicity if IFRT is administered after ASCR. In our experience, we found that a short, intensive course of IFRT (administered within 10 days) does not delay the time to ASCR (90% underwent ASCR within 1 month of starting IFRT), and is also safe. Furthermore, the preference at MSKCC has been to administer IFRT before transplant to obtain as minimal disease state as possible before ASCR, because this can determine a long-term PFS. Also, by administering IFRT before ASCR, patients are ensured that they will receive IFRT as part of their treatment regimen. This is not the case in patients planning to receive post-ASCR IFRT, because relapse shortly after transplant or significant hematologic or pulmonary toxicities after ASCR could prevent the delivery of IFRT. Furthermore, we hypothesize that a higher likelihood of MDS/leukemia could occur in patients receiving IFRT after transplant compared with before transplant because of exposing newly infused stem cells to radiation. This is avoided with pretransplant IFRT.

Thus far, we have witnessed a relatively low number of associated second malignancies (including MDS and AML), and only one patient developed a solid tumor within the IFRT field. However, treatment-related MDS and AML have been associated with IFRT in other studies. Kalaycio et al reported on 20 patients (4% of those transplanted) who developed treatment-related MDS/AML. They found that IFRT was a significant prognostic factor. Friedberg et al reported 13% of IFRT patients developed secondary MDS compared with 6.5% not receiving IFRT (P = .02). Our results contradict these findings; only 2% of patients developed MDS or AML, similar to the number found in studies without IFRT. Furthermore, half of those patients who developed MDS relapsed and died as a result of DLCL. Other factors, including prior exposure to alkylating agents and more extensive use of radiation, may explain the conflicting results. Although 49% of our patients have been observed for more than 5 years, longer follow-up is still necessary.

### Table 5. Adverse Prognostic Factors Based on Univariate and Multivariate Analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Overall Survival</th>
<th>Progression-Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Univariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage stage III or IV</td>
<td>1.8</td>
<td>1.1 to 2.9</td>
</tr>
<tr>
<td>Extracranial sites</td>
<td>1.7</td>
<td>1.0 to 2.7</td>
</tr>
<tr>
<td>ECOG PS ≥ 2</td>
<td>2.0</td>
<td>1.0 to 3.7</td>
</tr>
<tr>
<td>sAAIPI at salvage score &gt;2</td>
<td>1.8</td>
<td>1.1 to 3.0</td>
</tr>
<tr>
<td>Stem-cell source: bone marrow</td>
<td>2.1</td>
<td>1.2 to 3.8</td>
</tr>
<tr>
<td>Multivariate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage stage III or IV</td>
<td>2.0</td>
<td>1.2 to 3.3</td>
</tr>
<tr>
<td>Stem-cell source: bone marrow</td>
<td>2.4</td>
<td>1.3 to 4.3</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; ECOG PS, Eastern Cooperative Oncology Group performance score; sAAIPI, adjusted International Prognostic Index score before salvage therapy.

*Bone marrow was not significant for progression-free survival and was therefore not included in the table.
Our comprehensive, combined-modality treatment approach resulted in 5-year OS of 57% and PFS of 52%. These outcomes compare favorably with other large studies of patients with relapsed or refractory lymphoma undergoing HDT/ASCR. However, when IFRT has been added to the treatment of relapsed or refractory lymphoma undergoing HDT/ASCR, it has been shown to increase the rate of MDS/AML when compared with other non-IFRT-containing ASCT regimens. Important prognostic factors include patient stage before salvage therapy.

The way to show the benefits of IFRT in a salvage regimen is with a properly powered, prospectively randomized study. Unfortunately, a study designed by the National Cancer Institute of Canada Clinical Trials Group (Study LY8) closed because of poor accrual (R. Tsang, personal communication, June 2007).

Although recognizing the limitations of retrospective data, we nonetheless recommend that patients with bulky or residual disease limited to one or two sites after standard-dose salvage chemotherapy should be strongly considered for pre-HDT IFRT to safely reduce their risk for relapse.

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REFERENCES


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