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CLINICAL INVESTIGATION **Lymphoma**

INVOLVED FIELD RADIATION AFTER AUTOLOGOUS STEM CELL TRANSPLANT FOR DIFFUSE LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA

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Purpose: For patients with recurrent or refractory large B-cell non-Hodgkin's lymphoma, high-dose chemotherapy and autologous stem cell transplant (ASCT) is the treatment of choice. We evaluated the role of involved field radiation therapy (IFRT) post-ASCT for patients initially induced with cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or, more recently, rituximab-CHOP (R-CHOP).

Materials and Methods: Between May 1992 and April 2005, 176 patients underwent ASCT for recurrent or refractory large B-cell non-Hodgkin's lymphoma; 164 patients were evaluable for endpoint analysis. Fifty percent of the CHOP group (n = 131), and 39% of the R-CHOP group (n = 33), received IFRT. Follow-up from the time of transplant was a median/mean of 1.7/3 years (range, 0.03-13 years).

Results: The 5-year overall survival (OS) and disease-specific survival (DSS) improved with IFRT in both the R-CHOP (p = 0.006 and 0.02, respectively) and CHOP (p = 0.02 and p = 0.04, respectively) groups. IFRT was associated with a 10% (p = 0.17) reduction in local failure, alone or with a distant site. On univariate analysis, IFRT was associated with superior OS (hazard ratio [HR] = 0.50 [95% CI 0.32, 0.78]; p = 0.002) and DSS (HR = 0.53 [95% CI 0.33, 0.86]; p = 0.009). Presence of B symptoms was adverse (p = 0.03). On multivariate analysis, only IFRT was associated with significant improvement in OS (HR = 0.35 [0.18, 0.68]; p = 0.002) and DSS (HR = 0.39 [95% CI 0.18, 0.84]; p = 0.01).

Conclusions: Recognizing that positive and negative patient selection bias exists for the use of IFRT post-ASCT, patients initially treated with CHOP or R-CHOP and who undergo ASCT for recurrent or refractory disease may benefit from subsequent IFRT presumably due to enhanced local control that can translate into a survival advantage. © 2010 Elsevier Inc.

Diffuse large B-cell lymphoma, ASCT, Rituximab, R-CHOP, IFRT.

INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) accounts for 40% of all newly diagnosed cases of non-Hodgkin's lymphoma (NHL) (1). With combination chemotherapy like cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) (2), about 50% of patients achieve long-term survival (3). Despite the success of initial chemotherapy, a significant percentage of patients will manifest primary refractory disease or relapse after achieving a complete response (CR). For this group of patients, high-dose chemotherapy (HDC) followed by autologous stem cell transplantation (ASCT) provides significant improvement in outcome compared to conventional salvage chemotherapy (4).

Even though about 40 to 50% of patients with chemotherapy-sensitive relapse and 30% of patients with primary refractory disease will achieve long-term disease-free survival following ASCT, disease recurrence in previously involved sites accounts for the majority of subsequent failures (5). Involved-field radiotherapy (IFRT) has been used as an adjunct to ASCT in order to improve local control (6-8).

Recently, rituximab, a chimeric monoclonal anti-CD20 antibody in combination with CHOP has yielded an overall response rate of over 94% and has become the standard therapy for newly diagnosed cases of DLBCL (9). For patients with primary refractory disease or those for whom therapy fails after initial CR with rituximab-CHOP (R-CHOP), ASCT is the accepted salvage therapy although its benefit in this setting is not as well documented. Until now, no study has been done to assess the impact of IFRT posttransplant in the R-CHOP era.

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We previously demonstrated an improved disease-specific survival (DSS) and overall survival (OS) for IFRT following ASCT for aggressive NHL in the pre-rituximab era (10). The biology of DLBCL might be more aggressive in patients who fail R-CHOP since it is considered to be a more effective therapeutic approach. We hypothesized that IFRT post-ASCT might also be important for these patients.

METHODS AND MATERIALS

The University of Rochester Research Subjects Review Board approved our investigation. The study population included 176 patients (age 15.5 to 72 years) with biopsy results-proven diffuse large B-cell lymphoma who underwent HDC and autologous bone marrow or peripheral stem cell transplant between May 1992 and April 2005. Four (2%) of these patients underwent ASCT as an adjuvant to primary induction therapy, while the remainder underwent ASCT for recurrent or refractory disease. Patients were designated as refractory ($n = 58$ [33%]) if they never achieved a CR following initial therapy or relapsed ($n = 114$ [65%]) if at least one CR was achieved prior to ASCT. Twelve patients were excluded for endpoint analysis because they were managed posttransplant at outside institutions and their radiation status could not be determined. For the analysis of patterns of failure (*i.e.*, sites of recurrence post-ASCT), an additional three patients were excluded due to insufficient data.

All patients received conventional induction chemotherapy with CHOP. Since 2001, patients with DLBCL at our institution have also received rituximab as the initial therapy. All refractory/relapsed patients received salvage chemotherapy in order to achieve maximum possible cytoreduction prior to undergoing their transplant. The most commonly used salvage regimens were rituximab plus ifosfamide, carboplatin, and etoposide (R-ICE); cytosine, arabinoside, cisplatin, and dexamethasone (DHAP); or etoposide, cytarabine, cisplatin, and methylprednisolone (ESHAP). In recent years, R-ICE was the regimen used most frequently. The high-dose conditioning therapy included either BCNU, etoposide, 1-β-d-arabinofuranosylcytosine (ara-C), and cyclophosphamide (BEAC) or 1, 3-bis (2-chloroethyl)-1-nitrosourea (BCNU), etoposide, ara-C, and melphalan (BEAM). In the past 5 years, BEAM has been the therapy most frequently used. Fifteen patients received a myeloablative total body irradiation-based regimen. The dose for total body irradiation varied from 12 to 14 Gy with twice daily fractionation schemes. Following HDC, all patients received either an autologous bone marrow or peripheral stem cell infusion.

Patients were routinely evaluated for post-ASCT IFRT, with the possible exception of those who had relapsed in multiple organ sites. Patients were selected for post-ASCT IFRT based on several factors, including the number and volume of sites of disease at initial diagnosis and at recurrence, a history of previous irradiation and its dose/volume, and the expected morbidities of administering IFRT. Some patients might not have been referred for post-ASCT IFRT because they were expected to have a very favorable prognosis and thus would not require additional therapy, or because they were expected to have a poor prognosis and should not undergo the potential morbidities and inconvenience of IFRT. The decision to administer posttransplant IFRT was made jointly by the radiation oncologist (usually LSC) and the medical oncologist after consideration of these factors. For patients treated with IFRT post-ASCT, it was delivered as soon as the patient recovered from the acute side effects of HDT and, ideally, within 8 weeks after stem cell infusion. Patients with a CR to salvage chemotherapy generally received 20 to 26 Gy, patients with visible imaging abnormalities at ASCT received 30 Gy, and patients with persistent imaging abnormalities post-ASCT received 30 to 36 Gy. Total radiation doses and treatment schedules were individualized for each patient depending on the sites and volumes of disease at initial diagnosis and at relapse. Consideration was given to previous radiotherapy and to the radiosensitivity of normal tissues and organs that would be inadvertently irradiated. Radiation treatment volumes were localized to encompass the known site(s) of disease recurrence, and no specific attempt was made to include adjacent lymph nodal stations prophylactically; however, lymph node chains harboring sites of recurrence were irradiated if this was thought to be tolerable to the patient, as judged by the volume of bone marrow that might be exposed and other medical problems. All sites of initial disease involvement were generally treated in patients who experienced recurrence soon after primary therapy.

Data were summarized as medians, means, and proportions. Survival time was calculated from the date of stem cell infusion. For OS, death from any cause was scored as an event, whereas for DSS, only death from lymphoma or from toxicity was scored as an event. The distribution of OS and DSS times were estimated using the Kaplan-Meier method. Comparisons of survival times across groups were conducted using log-rank tests. Univariate and multivariate Cox proportional analyses were performed to investigate the influence of independent variables on these survival times. All p values smaller than 0.05 were considered significant. All statistical analyses were conducted using SAS version 9.1 software (SAS Institute Inc., Cary, NC).

RESULTS

The mean time from initial diagnosis to ASCT in the CHOP group was 2.5 years (range, 0.06–16.4 years), compared with 1.24 years (0.3–4.2 years) in the R-CHOP group ($p = 0.01$). The disease characteristics at initial diagnosis for the IFRT+ and no-IFRT groups are shown in Table 1. The median age at ASCT of patients who received IFRT posttransplant was 44 years compared to a median age of 52 years without IFRT ($p = 0.008$). Patients who presented with bulky disease were more likely to receive IFRT ($p = 0.04$). Sex, stage of disease, B symptoms (unexplained fever [i.e., temperature >38°C], weight loss exceeding 10% of body weight in 6 months, and drenching night sweats), and prior rituximab therapy were comparable in both groups. The median time to deliver IFRT following stem cell infusion was 55 days (range, 19–147 days). The median/mean follow up was 1.7/3 years (range, 0.03–13 years). Seventy-one out of 94 patient deaths resulted from recurrent lymphoma.

As shown in Fig. 1, the 5-year OS and DSS for the entire cohort was 45% and 50%, respectively. OS and DSS rates were determined for patients treated with R-CHOP and CHOP at diagnosis and stratified according to whether IFRT was administered post-ASCT. Kaplan-Meier curves of OS and DSS stratified by IFRT and rituximab are presented in Fig. 2. For both OS and DSS, there was a statistically significant difference among all four groups. In order to confirm whether the addition of IFRT improved the survival in both the R-CHOP and the CHOP groups, we calculated the survival by Kaplan-Meier separately stratified by IFRT; again, significance levels were met ($p = 0.0069$ and $p = 0.0203$, respectively). For the CHOP group, the median