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CLINICAL INVESTIGATION **Lymphoma**

TOTAL BODY IRRADIATION COMPARED WITH BEAM: LONG-TERM OUTCOMES OF PERIPHERAL BLOOD AUTOLOGOUS STEM CELL TRANSPLANTATION FOR NON-HODGKIN'S LYMPHOMA

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Purpose: The optimal preparative regimen for non-Hodgkin's lymphoma patients undergoing autologous peripheral blood stem cell transplantation (PBSCT) is unknown. We compared a total body irradiation (TBI)-based regimen with a chemotherapy-alone regimen.

Methods and Materials: A retrospective cohort study was performed at a Canadian cancer center. The TBI regimen consisted of cyclophosphamide, etoposide, and TBI 12 Gy in six fractions (CY/E/TBI). The chemotherapy-alone regimen consisted of carmustine, etoposide, cytarabine, and melphalan (BEAM). We compared the acute and long-term toxicities, disease relapse-free survival, and overall survival (OS).

Results: Of 73 patients, 26 received CY/E/TBI and 47 received BEAM. The median follow-up for the CY/E/TBI group was 12.0 years and for the BEAM group was 7.3 years. After PBSCT, no differences in acute toxicity were seen between the two groups. The 5-year disease relapse-free survival rate was 50.0% and 50.7% in the CY/E/TBI and BEAM groups, respectively ($p = .808$). The 5-year OS rate was 53.9% and 63.8% for the CY/E/TBI and BEAM groups, respectivey ($p = .492$). The univariate analysis results indicated that patients with Stage IV, with chemotherapy-resistant disease, and who had received PBSCT before 2000 had inferior OS. A three-way categorical analysis revealed that transplantation before 2000, rather than the conditioning regimen, was a more important predictive factor of long-term outcome ($p = .034$).

Conclusion: A 12-Gy TBI-based conditioning regimen for PBSCT for non-Hodgkin's lymphoma resulted in disease relapse-free survival and OS similar to that after BEAM. PBSCT before 2000, and not the conditioning regimen, was an important predictor of long-term outcomes. TBI was not associated with more acute toxicity or pneumonitis. We found no indication that the TBI regimen was inferior or superior to BEAM. © **2010 Elsevier Inc.**

Non-Hodgkin's lymphoma, total body irradiation, peripheral blood stem cell transplantation, BEAM regimen, interstitial pneumonitis.

INTRODUCTION

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) prolongs survival and might cure certain subsets of patients with relapsed or primary progressive non-Hodgkin's lymphoma (NHL). This is particularly applicable to aggressive subtypes of NHL (1, 2), although patients with indolent NHL might also benefit from ASCT (2, 3).

Total body irradiation (TBI)-based preparative regimens for bone marrow transplantation in humans with acute leukemia was first reported in the 1960s (4). TBI-based ASCT for NHL has been performed since the 1970s (5, 6). Subsequently, multiple chemotherapy-only regimens were developed and accepted as safe and effective conditioning regimens in ASCT for NHL (7–9). Several studies comparing these conditioning regimens have been published. In 2001, Gutierrez-Delgado *et al*. (10) reported that no significant differences were found in the toxicities and outcomes between TBI-based and chemotherapy-only conditioning regimens in ASCT for NHL. Another group concluded that chemotherapy-only regimens were more efficacious than TBI-based conditioning for diffuse large cell lymphoma (11). Their study also found that the carmustine, etoposide, cytarabine, and melphalan (BEAM) regimen was superior to several other chemotherapy-only regimens. The results of these retrospective studies have suggested that TBI does not provide

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an advantage as a component of conditioning before ASCT in NHL. However, the early study might have had a selection bias in which a greater proportion of patients whose stem cells were collected from bone marrow had TBI, and TBI was performed at an earlier era than chemotherapy-alone conditioning (10, 11). In the absence of randomized controlled studies, the exact role of TBI as a part of the conditioning in ASCT for NHL is unclear.

METHODS AND MATERIALS

The Manitoba Blood and Marrow Transplant program has used ASCT since 1991 to treat NHL patients. Both TBI- and BEAM-based conditioning regimens have been used in the Manitoba Blood and Marrow Transplant program, with BEAM adopted later. To investigate the effect of TBI-based conditioning on the outcome of ASCT for NHL, a retrospective review of all NHL patients (both indolent and aggressive subtypes) who had undergone ASCT was undertaken. For the present study, we selected patients who had had stem cells collected from the peripheral blood rather than the bone marrow to eliminate a selection bias. The acute toxicities, treatment-related mortality, disease relapse-free survival (DFS), and overall survival (OS) of the two regimens were compared. The goal of the present study was to understand the role of TBI in autologous peripheral blood stem cell transplantation (PBSCT) for NHL patients.

The University of Manitoba Health Research Ethics Board approved the present study. The patient information was abstracted from the Manitoba Blood and Marrow Transplant database and from the paper and electronic charts housed at the CancerCare Manitoba and Health Sciences Centre (Winnipeg, MB, Canada). Indolent NHL included follicular lymphoma (including follicular large cell) and small lymphocytic lymphoma at the initial diagnosis. Aggressive NHL included diffuse large B cell, anaplastic large cell, mixed small/large cell, natural killer cell, mantle cell lymphoma, peripheral T cell, and diffuse large B cell transformed from indolent lymphoma. We recorded the interval from diagnosis to transplantation, number of chemotherapy regimens before transplantation, disease status at transplantation, and whether local radiotherapy had been administered. Precursor lymphoblastic lymphoma patients were not included in the present study.

Conditioning regimens

The cyclophosphamide/etoposide/TBI (CY/E/TBI) regimen consisted of cyclophosphamide 100 mg/kg × 1 dose on Day −2, etoposide 60 mg/kg × 1 dose on Day −4, and cytarabine 30 mg/m^2 (to a maximal dose of 70 mg) given intrathecally on Day −7. TBI was delivered in 2-Gy fractions twice daily on Days −7 to −5 for six fractions (total dose of 12 Gy) using lateral, opposed compensated, 23-MV photon beams. The dose rate was 10–25 cGy/min. The source-to-axis distance was 3.55 M. The patients sat on a couch and the upper arms were placed to act as additional compensators for the lungs. The dose was prescribed at the mid-plane at the umbilicus. The BEAM regimen consisted of carmustine 300 mg/m^2 × 1 dose on Day −6, etoposide 200 mg/m^2 every 12 h × 8 on Days −5 to −2, cytarabine 200 mg/m^2 every 12 h × 8 on Days −5 to −2, melphalan 140 mg/m^2 × 1 dose on Day −1.

Transplantation characteristics

The patients underwent peripheral stem cell collection after chemotherapy and granulocyte-colony-stimulating factor stem cell mobilization. The mean CD34 cell count at transplantation was 5.26 × 10^6/kg (range, 1.15–22.29 × 10^6/kg). All patients receiving PBSCT received granulocyte-colony-stimulating factor 5 μg/kg from Day +5 until an absolute neutrophil count of ≥0.5 X10^9/L for 2 consecutive days was reached. All patients received fluconazole and ciprofloxicin prophylaxis from PBSCT until count recovery. Patients with positive pretransplant herpes simplex virus serology findings received acyclovir after PBSCT. The red blood cell and platelet transfusion threshold was <85 g/L and <10–20 × 10^9/L, respectively.

Acute toxicity grading

All toxicities identified through chart review were coded according to the Cancer Therapy Evaluation Program's Common Terminology Criteria for Adverse Events, version v3.0 (12). The interval to engraftment, febrile neutropenic events, major organ toxicities, and inpatient admission days were recorded. Interstitial pneumonitis (IP) was defined as pulmonary infiltrates on computed tomography scan without clinical or microbiologic evidence of an infectious etiology.

Study definitions

The pretransplant disease status was categorized as follows. Complete remission (CR) was defined as the complete disappearance of all known disease for >4 weeks. Chemotherapy-sensitive disease was defined as no CR but partial remission during treatment. Chemotherapy-resistant disease was defined as no CR but stable or progressive NHL during treatment (13). The previous number of treatments was defined as the number of regimens of chemtherapy a patient had received before transplant, excluding the conditioning regimen, and did not include local radiotherapy. Hematologic engraftment was defined as an absolute neutrophil count >0.5 × 10^9/L and platelet count >20 × 10^9/L.

Statistical analysis

The chi-square test, the median test, and Fisher's exact test were used for univariate comparisons. DFS was defined as the interval between the date of transplant and the date of relapse or death from any cause. OS was defined as the interval between the date of transplantation and the date of death from any cause. DFS and OS were calculated using the Kaplan-Meier method and were compared according to treatment group using the log–rank test. Statistical Analysis Systems, version 9.1 (SAS Institute, Cary, NC) was used.

Several factors were tested by univariate Cox proportional hazard modeling on outcomes, including gender (male vs. female), histologic type (indolent vs. aggressive), stage at diagnosis (Stage I-III vs. IV), B symptoms at diagnosis (negative vs. positive), lactate dehydrogenase at transplantation (<200 vs. >200 IU), pretransplant disease status (CR or sensitive vs. resistant), number of chemotherapy regimens before transplantation (<3 vs. ≥3), disease duration before transplant (<2 vs. ≥2 years) , transplant year (before 2000 vs. 2000 or after), and conditioning regimen. A three-way Cox regression model, including year of transplant and regimen, was created to clarify the effect of the year of transplantation on our results with BEAM.

RESULTS

Patients

Between March 1994 and September 2005, 73 patients received either BEAM (n = 47) or CY/E/TBI (n = 26)