Mortality Patterns Among Recipients of Autologous Hematopoietic Stem Cell Transplantation for Lymphoma and Myeloma in the Past Three Decades

Vijaya Raj Bhatt,[1] Fausto R. Loberiza, Jr,[1] Hongmei Jing,[2] R. Gregory Bociek,[1] Philip J. Bierman,[1] Lori J. Maness,[1] Julie M. Vose,[1] James O. Armitage,[1] Mojtaba Akhtari[1]

Abstract

We performed a retrospective study of patients with lymphoma and myeloma, aged ≥ 18 years, who had undergone autologous stem cell transplantation (ASCT) from 1983 to 2010 at the University of Nebraska Medical Center. Of the 2284 patients, 972 died within the first 5 years after ASCT. Disease relapse (73.4%), organ failure (7.8%), infection (4.7%), and secondary malignancy (4.2%) accounted for most of the deaths. The risk of death from infection (*P* < .0001), but not from relapse (*P* = .26), organ failure (*P* = .68), or secondary malignancy (*P* = .15), declined in the more recent cohorts. The mortality from relapse remained the most common cause of death.

Background: Understanding the mortality patterns of patients with lymphoma and myeloma, who have undergone autologous hematopoietic stem cell transplantation (ASCT) might identify improvement opportunities. **Patients and Methods:** The present retrospective study included patients with lymphoma and myeloma, aged ≥ 18 years, who had undergone ASCT from 1983 to 2010 at the University of Nebraska Medical Center. Of the 2284 patients, 972 had died within first 5 years after ASCT. The patients were divided into 3 cohorts according to the time of transplantation: 1983 to 1990 (cohort I), 1991 to 2000 (cohort II), and 2001 to 2010 (cohort III). Using Cox proportional hazards regression analysis, the risk of cause-specific mortality was compared across the 3 cohorts. **Results:** Of a total of 1215 deaths, 972 (80%) occurred within the first 5 years after ASCT. Disease relapse (73.4%), organ failure (7.8%), infection (4.7%), and secondary malignancy (4.2%) accounted for most of the deaths. The risk of death from infection ($P < .0001$), but not from relapse ($P = .26$), organ failure ($P = .68$), or secondary malignancy ($P = .15$), had declined in the more recent cohorts. **Conclusion:** The 5-year overall survival of patients undergoing ASCT has improved significantly owing to a decline in infectious mortality. Our results highlight that the mortality from relapse remains the most common cause of death, warranting investigation of different strategies to reduce the incidence of relapse and improve the therapy for relapse after ASCT.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 15, No. 7, 409-15
Keywords: Autologous stem cell transplantation, Causes of death, Hodgkin lymphoma, Multiple myeloma, Non-Hodgkin lymphoma

Introduction

High-dose chemotherapy, followed by autologous hematopoietic stem cell transplantation (ASCT), improves overall survival (OS) in patients with relapsed non-Hodgkin lymphoma (NHL).[1-6] ASCT also improves progression-free survival in patients with mantle cell lymphoma[7,8] and relapsed Hodgkin lymphoma (HL).[9-11] In some

[1]Division of Hematology-Oncology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE
[2]Department of Hematology, Third Hospital, Peking University, Peking, China

Submitted: Nov 20, 2014; Revised: Feb 13, 2015; Accepted: Feb 26, 2015; Epub: Mar 5, 2015

Address for correspondence: Mojtaba Akhtari, MD, Division of Hematology-Oncology, Department of Internal Medicine, University of Nebraska Medical Center, 987680 Nebraska Medical Center, Omaha, NE 68198
E-mail contact: mojtaba.akhtari@unmc.edu

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2015.02.024

of the initial trials, an OS benefit was seen with upfront ASCT in patients with multiple myeloma (MM).[12,13] However, whether an OS benefit with upfront ASCT in patients with MM still exists in the era of novel therapy is controversial. Recently, a large, phase III randomized trial of 273 patients with MM demonstrated improved OS with upfront consolidation with two 4-month cycles of high-dose melphalan and ASCT compared with 6 cycles of melphalan, prednisone, and lenalidomide.[14] That study demonstrated that upfront ASCT improves OS compared with consolidation with a lenalidomide-based regimen. However, that study did not use bortezomib or other novel agents in the induction or consolidation phase. Regardless, ASCT has been associated with improved outcomes in patients with relapsed MM.[15] The opportunity to improve the outcomes of patients with NHL, HL, and myeloma with ASCT has resulted in frequent use of ASCT to treat these diseases. Although the development of novel agents might change the practice patterns, ASCT is frequently used in patients with untreated MM and mantle cell lymphoma and those with relapsed NHL and HL.

During the past 3 decades, the field of ASCT has greatly evolved, with the use of a better tolerated high-dose regimen,[16,17] increased use of peripheral blood stem cell transplantation,[18] improvements in supportive care,[19-22] and a better understanding of transplant-related complications. Similar advances have occurred in other fields, such as transfusion medicine, critical care medicine, infectious disease, cardiology, and nephrology, among the many fields in medicine.[23-25] Collectively, such advancements have improved the outcomes with ASCT. Two large studies from the Center for International Blood and Marrow Transplant Research (CIBMTR) have demonstrated a significant improvement in the 5-year OS after ASCT for patients with MM and lymphoma, despite an increase among older patients in recent years.[26,27]

Although the outcomes of ASCT have certainly improved in recent years, the different factors that contribute to early mortality after ASCT remain poorly investigated. With these changes in the field of transplantation, we speculated that variation would be present in the causes of deaths in patients with lymphoma and MM within 5 years of ASCT. Understanding the causes of early mortality has implications in designing programs to further improve the outcomes for these patients. CIBMTR studies have already extensively reviewed the characteristics of the entire cohort of patients with MM and lymphoma who underwent ASCT and analyzed the survival trend.[26,27] Unlike these studies, in the present study, we determined the characteristics and causes of mortality of patients with MM and lymphoma, who had died within the first 5 years after ASCT in past 3 decades at a single tertiary care academic hospital.

Patients and Methods

Patient Population

The present study was a retrospective cohort study of consecutive patients, aged $\geq$ 18 years, with HL, NHL, or MM who had received their first ASCT from 1983 to 2010 at the University of Nebraska Medical Center (UNMC) and had died within the first 5 years after ASCT. The patients were grouped into 3 cohorts according to the time of transplantation: 1983 to 1990 (cohort I), 1991 to 2000 (cohort II), and 2001 to 2010 (cohort III). The transplantation database at UNMC includes the collected information from patients who had consented and had been treated inside or outside of a clinical trial. The information available in the transplant database includes demographic data, disease characteristics, therapy details, and outcomes. The primary cause of death was determined and verified by the transplant physician, who primarily treated the patient. The cause of death was determined from the clinical, laboratory, and radiological test results. The institutional review board at the UNMC approved the study.

Transplant Regimens

Before ASCT, all the patients had undergone a thorough evaluation, including a complete blood count, renal and liver function testing, bone marrow biopsy, and cardiopulmonary function tests. The common high-dose chemotherapy regimens for cohorts I and II included BEAC (BCNU [carmustine] 300 mg/m^2 on day -6, cytarabine 100 mg/m^2 twice a day on days -6 to -3, etoposide 100 mg/m^2 twice a day on days -6 to -3, and cyclophosphamide 35 mg/kg on days -6 to -3), CBV (cyclophosphamide 1.5 g/m^2 on days -6 to -3, BCNU 300 mg/m^2 on day -6, and etoposide 100 mg/m^2 every 12 hours for 6 doses on days -6 to -4), and Cy/TBI (cyclophosphamide 60 mg/kg on days -5 and -4 and total body irradiation 200 cGy twice daily for 6 doses on days -3 to -1).[28] Most recently, the treatment regimens included BEAM (BCNU 300 mg/m^2 on day -6, cytarabine 100 mg/m^2 twice a day on days -5 to -2, etoposide 100 mg/m^2 twice a day on days -5 to -2, and melphalan 140 mg/m^2 on day -1) for those with HL or NHL.[29] The common high-dose regimen for patients with MM in cohorts I and II was melphalan (200 mg/m^2 on day -1 or 140 mg/m^2 for patients with significant renal dysfunction or elderly patients).[30,31] Autologous stem cells, obtained from the bone marrow or the blood, or both, were reinfused intravenously on day 0 through a central venous catheter. Peripheral blood was used exclusively as the graft source beginning in the 1990s. Granulocyte colony-stimulating factor (CSF) was started on day +7. Granulocyte macrophage-CSF was administered from day 0 to some of the patients in the early cohorts. The growth factor was continued until neutrophil engraftment. The patients received supportive care, including blood product transfusion and antimicrobial prophylaxis, in accordance with the contemporary standard of care.

Statistical Analysis

The patient-, disease-, and treatment-related characteristics in the different cohorts of patients who died within the first 5 years after ASCT were compared using the χ^2 test or Kruskal-Wallis test for categorical and continuous data, respectively. Univariate probabilities of survival were estimated using the Kaplan-Meier method. The risk of dying from a particular cause (ie, relapse, infection, secondary malignancy, or organ failure) was compared across all the cohorts using Cox proportional hazards regression, with adjustment for age, gender, disease type, disease stage at transplantation, and interval from diagnosis to transplantation. This analysis included the proportion of deaths from different causes among all the transplanted patients. The assumption of proportionality was tested