Biol Blood Marrow Transplant 23 (2017) 1276–1281

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASBMT American Society for Blood and Marrow Transplantation

Prognostic Analysis of Absolute Lymphocyte and Monocyte Counts after Autologous Stem Cell Transplantation in Children, Adolescents, and Young Adults with Refractory or Relapsed Hodgkin Lymphoma

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Article history:
Received 14 February 2017
Accepted 14 April 2017

Key Words:
Hodgkin lymphoma
Autologous stem cell transplantation
Absolute lymphocyte count
Absolute monocyte count
Prognostic

A B S T R A C T

Previous studies in adults have shown that peripheral blood absolute lymphocyte and monocyte count ratio (ALC/AMC) after autologous stem cell transplantation (ASCT) can predict outcome in patients with relapsed/refractory (R/R) Hodgkin lymphoma (HL). We retrospectively reviewed all of our children, adolescent, and young adult (CAYA) patients (age ≤26) who underwent transplantation for R/R HL between 2004 and 2015. Seventy-six patients (median age, 21; range, 10 to 26 years) who reached day 100 disease free were analyzed; 33% of them had positron emission tomography (PET)–positive tumors before ASCT. Patients received high-dose carmustine, etoposide, cytarabine, and melphalan (n = 40) or gemcitabine/busulfan/melphalan (n = 36). Median follow-up after day 100 was 3.9 years (95% confidence interval [CI], 2.8 to 4.9). A day 100 ALC/AMC ratio >2.1 correlated with lower risk of relapse (hazard ratio, .097; 95% CI, .03 to .29; $P < .0001$). Patients with day 100 ALC/AMC ratios >2.1 and ≤2.1 had 4-year relapse-free survival rates of 93% and 33%, respectively ($P = .0001$) and 4-year overall survival rates of 96% and 76%, respectively ($P = .0001$). In addition, an ALC/AMC ratio increase >1.8 from day 15 to day 100 correlated with lower risk of relapse (hazard ratio, .24; 95% CI, .08 to 0.73; $P = .01$). Likewise, an ALC/AMC ratio change >.26 from day 30 to day 100 also correlated with a lower likelihood of relapse (hazard ratio, .20; 95% CI, .081 to .51; $P = .0007$). Multivariate analysis showed that a positive PET scan at ASCT, day 100 ALC/AMC ratio ≤ 2.1, and an ALC/AMC ratio change either ≤1.8 from day 15 to day 100 or ≤.26 from day 30 to day 100 were independent adverse predictors. In conclusion, our analysis confirms in CAYA patients prior observations in adults indicating a major prognostic effect of peripheral lymphocyte and monocyte counts at day 100 and earlier post-ASCT time points in R/R HL.

INTRODUCTION

Hodgkin lymphoma (HL) has a high cure rate. However, treatment of patients with relapsed or refractory (R/R) disease remains a challenge. High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is a mainstay of treatment of R/R HL. Recent insights into the biology of HL and its microenvironment [1] have set the stage for new effective therapies. For instance, it has been shown that tumor-associated macrophages are a strong prognostic indicator in HL [2-4] and that the specific phenotype of tumor-infiltrating lymphocytes is associated with outcome [5,6]. Previous studies in adults have found that absolute lymphocyte count (ALC), absolute monocyte count (AMC), and the ALC/AMC ratio obtained from the peripheral cell blood count (CBC) at diagnosis serve as a surrogate of this microenvironment and are independent prognostic markers of outcome for many malignancies, including HL [7-9]. More specifically, post-ASCT ALC/AMC ratio at day 100 predicts outcome of patients with R/R HL [10]. However, it is unclear which CBC metrics in the post-ASCT period are most representative of the HL microenvironment and predict relapse. Furthermore, the significance of the ALC, AMC, and ALC/AMC ratio has never

Financial disclosure: See Acknowledgments on page 1281.

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http://dx.doi.org/10.1016/j.bbmt.2017.04.013
1083-8791/

been evaluated in children, adolescents, and young adults (CAYA) undergoing ASCT. In this study we analyzed the prognostic significance of the ALC/AMC ratio on day 100 after ASCT and its change from day 15 or day 30 to day 100 in CAYA with R/R HL.

PATIENTS AND METHODS

We conducted a retrospective review of MD Anderson Cancer Center patients 26 years old or younger with R/R HL. Eligibility for this analysis included achievement of a complete remission by day 100 after ASCT. Approval for this retrospective chart review was obtained from the MD Anderson institutional review board.

The primary endpoint of the study was to evaluate the relationship between the patient outcomes of overall survival (OS) and relapse-free survival (RFS) and the ALC/AMC ratio on day 100 after transplantation. A secondary endpoint was to compare the effect of the change of ALC/AMC ratio from day 15 and day 30 to day 100 on OS and RFS. The ALC and AMC were obtained from CBCs collected on day 15, day 30, and day 100. The other covariates evaluated included age, sex, prior radiation therapy, prior primary/salvage chemotherapy, bulky disease at relapse (any lesion >5 cm), extranodal disease at relapse, presence of B symptoms at relapse, and positron emission tomography (PET)-computed tomography (CT) status immediately before ASCT.

We defined staging, response, and outcomes following the guidelines from the Lymphoma Imaging Working Group [11] and Harmonization Project in Lymphoma [12].

Statistical Analysis

A landmark analysis was used to estimate the effect of day 100 after ASCT on outcomes. The Wilcoxon rank-sum test or Kruskal-Wallis test, whichever appropriate, were used to examine the difference in ALC/AMC ratio at day 100 by the cutoff point between levels of covariates. The Kaplan-Meier survival analysis, including a log-rank test and Cox regression analysis, assessed the effect of categorical and continuous variables, respectively, on RFS and OS. The Contal and O'Quigley method was used to identify the optimal cutoff point of prognostic factors of interest for RFS and OS when the log-rank statistics was concerned [13]. The variables found to be significantly associated with the outcome of interest in the univariate analyses were included in the multivariate models. All computations used SAS 9.3 (SAS Institute, Inc., Cary, NC), Splus 8.2 (TIBCO Software, Inc, Palo Alto, CA), and R 3.1.3. Results were considered statistically significant when the P value was <.05.

RESULTS

We identified 76 consecutive CAYA patients meeting the analysis criteria. The median age at day 100 after ASCT was 21 (range, 10 to 26). Pre-ASCT salvage regimens included ifosfamide/carboplatin/etoposide (n = 32), etoposide/methylprednisolone/high-dose cytarabine/cisplatin (n = 20), ifosfamide/gemcitabine/vinorelbine (n = 14), gemcitabine/vinorelbine/liposomal doxorubicin (n = 7), or other (n = 3). Patients received a high-dose chemotherapy regimen of either carmustine, etoposide, cytarabine, and melphalan or gemcitabine, melphalan, and busulfan [14]. All patients received peripheral blood progenitor cells. The median follow-up beyond the first 100 days after ASCT was 3.86 years (95% confidence interval [CI], 2.81 to 4.85). Twelve patients died secondary to R/R HL after post-ASCT day 100. There were no transplantation-related deaths.

We detected the following prognostic cut-off points for OS and RFS: 1060 cells/uL for day 100 ALC, 760 cells/uL for day 100 AMC, and 2.1 for the day 100 ALC/AMC ratio (Figures 1 and 2). Sex, the presence of bulky mediastinal disease at the time of relapse, and the findings in the pretransplantation PET-CT scan evaluations were significantly different in patients with an ALC/AMC ratio ≤2.1 versus those with a ratio >2.1 (Table 1).

Patients with a day 100 ALC >1060 and ≤1060 cells/uL had RFS rates at 24 months of 86% and 59%, respectively, at 24 months, and 86% and 52%, respectively, at 48 months (P = .053) (Figure 1A). Their respective OS rates at 24 months were 96% and 83%, and at 48 months, 96% and 70% (P = .0001) (Figure 2A).

In addition, patients with a day 100 AMC ≤760 and >760 cells/uL had RFS rates at 24 months of 83% and 0%, and RFS rates at 48 months of 79% and 0%, respectively (P = .001) (Figure 1B). Their OS rates at 24 months were 95% and 52%, respectively, and at 48 months of 87% and 52%, respectively (P = .017) (Figure 2B).

Similarly, patients with a day 100 ALC/AMC ratio >2.1 had superior RFS rates to those with day 100 ALC/AMC ratio ≤2.1 (92% at both 24 and 48 months compared with 39.9% and 33% at 24 months and 48 months, respectively, P = .0001) (Figure 1C). Eleven of 30 patients (36.7%) in the group with a day 100 ALC/AMC ratio ≤2.1 died, compared with 1 death in 46 patients (2.2%) with a day 100 ALC/AMC ratio >2.1. Consequently, the OS rate of the patients with day 100 ALC/AMC ratio >2.1 was superior to that of patients with a ratio ≤2.1 (100% and 96% at 24 and 48 months, compared with 85% and 76% at 24 and 48 months, respectively, P = .0001) (Figure 2C).

We compared ALC, AMC, and ALC/AMC ratio on day 15 and day 30 in comparison to day 100 (Table 1). The RFS rates were superior in patients whose ALC/AMC ratios increased ≥1.8 points from day 15 to day 100 compared with those whose ALC/AMC ratios increased <1.8 points (RFS rate of 92% at both 24 and 48 months versus 56% and 52% at 24 and 48 months, respectively, P = .0056). An ALC/AMC ratio change >.26 from day 30 to day 100 correlated in a longer RFS compared to a ratio change ≤.26 (RFS: 84% at both 24 and 48 months versus 32% and 16% at 24 and 48 months, respectively, P < .0001).

Likewise, patients with larger ALC/AMC ratio increases from either day 15 or day 30 to day 100 had markedly improved RFS compared with patients with smaller ALC/AMC ratio increases (Figure 3A and B).

Univariate and Multivariate Analyses

Univariate analyses showed that the use of radiation therapy during initial treatment, 1 versus 2 salvage chemotherapy lines, absence of extranodal disease at relapse, absence of bulky disease at relapse, negative PET-CT scan results before ASCT, day 100 ALC >1060, day 100 AMC ≤760, day 100 ALC/AMC ratio >2.1, and changes in ALC/AMC ratios between day 15 and day 100 >1.8 or between day 30 and day 100 >.26, were significantly associated with longer RFS.

One versus 2 salvage chemotherapy lines before transplantation, absence of bulky disease at relapse, negative PET-CT scan results before ASCT, day 100 ALC >1060, day 100 AMC ≤760, day 100 ALC/AMC ratio >2.1, and changes in ALC/AMC ratios between day 15 and day 100 of >1.8 or between day 30 and day 100 >.26 were significantly associated with longer OS (Table 2).

Multivariate analyses showed that those values of day 100 ALC/AMC ratio, day 100 ALC, day 100 AMC, and changes in ALC/AMC ratio were all independent predictors for RFS. Likewise, day 100 ALC/AMC ratio >2.1 and a change in the ALC/AMC ratio from day 30 to day 100 >.26 independently predicted longer OS (Table 3).

Importantly, when using a Cox regression model and a hazard ratio analysis, regardless of which of our variables of interest (ALC/AMC ratio, ALC, AMC, and the differences in ratio) were included either for OS and RFS, having a positive PET-CT scan before ASCT and a day 100 ALC/AMC ratio ≤2.1 were always independently associated with significantly higher hazard ratios for both outcomes (Table 4).