Original Study

Comparison of Autologous Hematopoietic Cell Transplantation and Chemotherapy as Postremission Treatment in Non-M3 Acute Myeloid Leukemia in First Complete Remission

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Abstract

Randomized trials of acute myeloid leukemia (AML) in first complete remission (CR1) showed that autologous hematopoietic cell transplantation (auto-HCT) improves relapse-free survival (RFS) but not overall survival (OS), compared with chemotherapy. Using a database of 2518 adult patients with AML in CR1, we conducted a 5-month landmark analysis and found that auto-HCT improves 3-year RFS but not OS compared with chemotherapy.

Introduction: A number of randomized trials in patients with AML in CR1 have been conducted and they showed that auto-HCT improves RFS but not OS, compared with chemotherapy. However, because these trials have had compliance problems, the value of auto-HCT still has not been clearly established. **Patients and Methods:** Using a database of 2518 adult patients with AML in CR1, we retrospectively analyzed the outcome of auto-HCT and compared it with intensive nonmyeloablative chemotherapy using landmark analyses. **Results:** In 103 auto-HCT recipients, OS and RFS at 3 years from treatment were 65% and 57%, respectively. Multivariate analysis showed that unfavorable risk cytogenetics and entry into CR1 after 2 courses of induction treatment predicted a poor outcome. Because the median time interval between CR1 and auto-HCT was 153 days, landmark analyses at 5 months after CR1 were performed to compare 1290 patients who received chemotherapy alone (median age, 52 years; range, 16-70) with 103 who received auto-HCT (median age, 48 years; range, 16-67). Auto-HCT improves 3-year RFS (58% vs. 37%; $P < .001$) but not OS compared with chemotherapy alone. Among patients with unfavorable risk cytogenetics or those who required 2 courses to reach CR1, there was no significant difference in RFS between the 2 groups. **Conclusion:** Auto-HCT can be considered as a postremission therapy for AML patients with favorable or intermediate risk cytogenetics who achieve CR1 after a single course of induction treatment.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 12, No. 6, 444-51 © 2012 Elsevier Inc. All rights reserved.
Keywords: AML, Autologous transplantation, CR1, inv(16), Postremission therapy, t(8;21)

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Submitted: Mar 12, 2012; Revised: Jun 19, 2012; Accepted: Jul 26, 2012; Epub: Sept 20, 2012

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2152-2650/$ - see frontmatter © 2012 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.clml.2012.07.004

Introduction

Autologous hematopoietic cell transplantation (auto-HCT) has been investigated as a potential therapeutic option to improve the outcome in acute myeloid leukemia (AML) patients. However, its value in the treatment of adults in remission has not been clearly established. Compared with allogeneic hematopoietic cell transplantation (HCT), auto-HCT offers the possibility of performing the same myeloablative regimen without the risks associated with graft-versus-host disease. Though the toxic death rate in auto-HCT is much lower than that in allogeneic HCT, the relapse rate remains higher[1-6] because of either graft contamination by malignant cells[7] or the absence of a graft-versus-leukemia effect by donor lymphocytes. To date, randomized trials in patients with AML in first complete remission (CR1) have been conducted to compare the postremission strategies of intensive chemotherapy, allogeneic HCT, and auto-HCT.[8-19] All of these trials analyzed the outcome on an intention-to-treat basis, and only 66% of patients actually underwent the intended auto-HCT treatment.[2-4,20] This can clearly pose problems in interpretation when a significant proportion of patients do not actually undergo the intended treatment.[19] On the other hand, despite the limitations of biases that might be difficult or impossible to identify and/or adjust for, observational databases contain information on large numbers of diverse subjects who have received diverse therapies, and can be analyzed to potentially provide answers that are more useful to clinicians than those obtained from randomized controlled trials.[21]

In the present study, we used a database of 2518 adult AML patients who achieved CR1 to retrospectively compare auto-HCT with intensive nonmyeloablative chemotherapy in AML patients in CR1.

Patients and Methods

Data Source

We created a nation-wide database of AML patients in CR1.[22] The targeted patients were adults aged 16-70 years who had been diagnosed with AML between 1999 and 2006, and who had achieved CR1 after 1 or 2 courses of induction chemotherapy. The diagnosis of AML was determined according to the World Health Organization classification fourth edition.[23,24] The National Cancer Center Hospital's institutional review board approved the protocol. Clinical data for more than 2600 patients were collected from 70 institutions between June and December 2008. Among them, patients with acute biphenotypic leukemia who were treated with chemotherapy for acute lymphocytic leukemia and those who had extramedullary AML without marrow invasion, or extramedullary lesions that did not totally disappear after remission-induction chemotherapy were excluded. In this study, patients with acute promyelocytic leukemia and those who received allogeneic HCT in CR1 were also excluded. Information about the disease risk at diagnosis, clinical course, and conditioning regimen for auto-HCT were collected.

Statistical Analysis

Data were retrospectively reviewed and analyzed as of April 2010. The primary end point of the study was overall survival (OS) with respect to either auto-HCT or CR1. The unadjusted probabilities of OS, relapse-free survival (RFS), and relapse rate were estimated using the Kaplan–Meier product limit method. OS, RFS, and the incidence of relapse were estimated as probabilities at 3 years after either auto-HCT or CR1. The log-rank test was used to compare the probabilities among different subgroups. The Cox proportional hazards regression model was used to estimate relative hazard ratios for OS, RFS, and the incidence of relapse. As covariates, we considered age, sex, conditioning regimen, interval from CR1 to auto-HCT, cytogenetic risks according to the Southwest Oncology Group (SWOG)[25], French-American-British (FAB) classifications,[24,26-29] number of courses of chemotherapy required to achieve CR1, white blood cell (WBC) count, and antecedent hematological disorders or dysplasia at diagnosis. We judged 2-tailed P values $< .05$ to be statistically significant. Statistical analyses were performed with SPSS software version 11.0.1 (SPSS, Chicago, IL).

Results

Patient Characteristics

We excluded 494 patients who had received allogeneic HCT in CR1 and 386 acute promyelocytic leukemia patients from the total of 2518 patients. Table 1 summarizes the characteristics of the remaining 1638 patients. Auto-HCT was used to treat 103 patients (auto-HCT group), and the other 1535 were treated with chemotherapy alone (chemotherapy group). Median follow-up times for the total test population and auto-HCT group were 50 months (0.2-116 months) and 60 months (6-115 months), respectively.

The proportions of patients in the auto-HCT group with favorable, intermediate, unfavorable, and unknown risk cytogenetics according to the SWOG criteria were 26%, 49%, 17%, and 9%, respectively. These values were not significantly different from those in patients who were treated with chemotherapy alone. As a remission induction therapy, 95% or more of patients in both groups had received standard-dose cytarabine and anthracycline (daunorubicin or idarubicin) -based regimen. Consolidation therapy was continued with cytarabine-based regimens with or without maintenance therapy at the discretion of physicians.

There was no significant difference in FAB subtypes, the number of remission-induction therapies, or the WBC count at the time of diagnosis between the 2 groups. However, the proportion of patients who had antecedent hematological disorders or dysplasia at diagnosis was significantly lower in auto-HCT patients than in chemotherapy patients ($P = .011$). Auto-HCT patients were significantly younger than the chemotherapy patients ($P = .006$).

Among auto-HCT patients, 62 (70%) received granulocyte colony stimulating factor (G-CSF) combined with BEA (busulfan/etoposide/cytosine arabinoside)[30,31] as a conditioning regimen: busulfan (4 mg/kg per day, 1 mg/kg per dose, 4 times a day [days −9 to −6], for 16 doses), etoposide (20 mg/kg on days −5 to −4), cytarabine (100 mg/m^2 on days −10 to −4, 3 g/m^2 every 12 hours on days −3 to −2), and filgrastim (200 μg/m^2 on days −12 to −4). The median time interval between CR1 and transplantation was 153 days (21-749 days). Only 8 patients (8%) received transplants within 100 days after reaching CR1, and approximately half of the patients (n = 55; 53%) underwent transplantation between 101 and 180 days after CR1.