Biol Blood Marrow Transplant 20 (2014) 1369–1374

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Early versus Late Preemptive Allogeneic Hematopoietic Cell Transplantation for Relapsed or Refractory Acute Myeloid Leukemia

George L. Chen [1], Hong Liu [1], Yali Zhang [1], Julie Thomas [1], Maureen Ross [1], Eunice S. Wang [2], AnneMarie W. Block [3], Sheila Sait [3], George Deeb [4], Paul Wallace [5], Meir Wetzler [2], Theresa Hahn [1], Philip L. McCarthy [1,*]

[1] *Department of Medicine, BMT Program, Roswell Park Cancer Institute, Buffalo, New York*
[2] *Department of Medicine, Leukemia Division, Roswell Park Cancer Institute, Buffalo, New York*
[3] *Clinical Cytogenetics Laboratory, Roswell Park Cancer Institute, Buffalo, New York*
[4] *Department of Pathology, Roswell Park Cancer Institute, Buffalo, New York*
[5] *Department of Flow Cytometry, Roswell Park Cancer Institute, Buffalo, New York*

Article history:
Received 20 March 2014
Accepted 9 May 2014

Key Words:
Relapsed or refractory AML
Hypoplasia
Allogeneic hematopoietic cell transplant

A B S T R A C T

Many patients with relapsed or refractory acute myeloid leukemia (AML) do not receive allogeneic hematopoietic cell transplantation (alloHCT) because they are unable to achieve a complete remission (CR) after reinduction chemotherapy. Starting in January 2003, we prospectively assigned patients with AML with high-risk clinical features to preemptive alloHCT (p-alloHCT) as soon as possible after reinduction chemotherapy. High-risk clinical features were associated with poor response to chemotherapy: primary induction failure, second or greater relapse, and first CR interval <6 months. We hypothesized that any residual disease would be maximally reduced at the time of transplant, resulting in the best milieu and most lead time for developing a graft-versus-leukemia effect and in improved long-term overall survival (OS) without excess toxicity. This analysis studied the effect of transplant timing on p-alloHCT in 30 patients with high-risk clinical features of 156 consecutive AML patients referred for alloHCT. We compared early p-alloHCT within 4 weeks of reinduction chemotherapy before count recovery with late p-alloHCT 4 weeks after reinduction chemotherapy with count recovery. OS and progression-free survival (PFS) at 2 years were not significantly different for early versus late p-alloHCT (OS 23% versus 33%, respectively, $P > .1$; PFS 18% versus 22%, respectively, $P > .1$). Day 100 and 1-year transplant-related mortality were similar (33.3% versus 22.2%, $P > .1$; 44.4% versus 42.9%, $P > .1$, respectively). Preemptive alloHCT allowed 30 patients to be transplanted who would normally not receive alloHCT. Clinical outcomes for early p-alloHCT are similar to those for late p-alloHCT without excess toxicity. Early p-alloHCT is a feasible alternative to late p-alloHCT for maximizing therapy of AML that is poorly responsive to induction chemotherapy.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) for poor-prognosis acute myeloid leukemia (AML) has been performed after achieving a complete remission (CR) to consolidate a patient's response to chemotherapy and prevent future relapse. Many patients, however, will not receive an alloHCT because they are unable to achieve a CR because of chemotherapy resistant or rapidly progressive disease. The overall clinical benefit of alloHCT in patients not in CR is uncertain because any nascent graft-versus-leukemia effects may be overtaken by expanding residual disease and gains from disease control may be outweighed by transplant-related complications.

Residual leukemia is a contraindication to alloHCT in some transplant centers. An alternative approach is to perform alloHCT preemptively (p-alloHCT) after induction chemotherapy. In this setting, any residual disease has been maximally treated, allowing the donor graft the best chance to initiate a graft-versus-leukemia effect and overcome the kinetics of disease progression. Because alloHCT requires advance planning, it is often not possible to make decisions about proceeding with p-alloHCT based on a late restaging pretransplant bone marrow biopsy. Therefore, starting in

Financial disclosure: See Acknowledgments on page 1374.

* Correspondence and reprint requests: Philip L. McCarthy, MD, Roswell Park Cancer Institute, Department of Medicine, Elm & Carlton Streets, Buffalo, NY 14263.
E-mail address: philip.mccarthy@RoswellPark.org (P.L. McCarthy).

1083-8791/$ – see front matter © 2014 American Society for Blood and Marrow Transplantation.
http://dx.doi.org/10.1016/j.bbmt.2014.05.013

January 2003, the Roswell Park Cancer Institute Blood and Marrow Transplant and Leukemia services made a programmatic decision to prospectively treat all AML patients with high-risk clinical features predictive of not achieving a CR with p-alloHCT. These high-risk clinical features were defined as primary induction failure, second or greater relapse, and first CR interval <6 months. Because alloHCT soon after induction chemotherapy may be associated with fatal toxicity, we analyzed the effect of p-alloHCT timing on safety, feasibility, and clinical effect of alloHCT in 30 AML patients with high-risk clinical features.

METHODS

Disease, Response, and Treatment Group Definitions

AML was diagnosed according to the World Health Organization and French-American-British classification schemes [1-3]. Cytogenetic risk was categorized according to Eastern Cooperative Oncology and Southwest Oncology Group criteria: good risk (inv16, t[8;21], t[15;17]), poor risk (−5/del[5q], −7/del[7q], inv[3q], abn11q, 20q or 21q, del[9q], t[6;9], t[9;22], abn17p, and complex karyotype defined as three or more abnormalities), and intermediate risk (other and normal karyotypes) [4].

Early p-alloHCT was performed within 4 weeks of induction or reinduction chemotherapy before count recovery regardless of restaging bone marrow histopathology. Late p-alloHCT was performed after count recovery and >4 weeks after prior chemotherapy. Count recovery was defined as an absolute neutrophil count $>1 \times 10^9$/L and a platelet count $>100 \times 10^9$/L.

Bone marrow biopsies were performed ≤2 weeks before graft infusion to assess disease status. CR was defined as a normocellular bone marrow containing <5% blasts with count recovery. A hypoplastic bone marrow was defined as <20% bone marrow cellularity with <5% blasts. A refractory bone marrow was defined as ≥5% blasts, regardless of cellularity.

Patient Population

From January 2003 to March 2008, 156 consecutive adult AML patients were referred to the Roswell Park Cancer Institute Blood and Marrow Transplant program for alloHCT evaluation. Eighty-four of 156 patients (54%) did not receive alloHCT for reasons presented in Table 1. Seventy-two of 156 patients (46%) received alloHCT; 30 of these 72 were at high risk for not achieving a CR after induction chemotherapy based on the following risk factors: primary induction failure, beyond first relapse, or remission interval <6 months. In this report, these patients, who were at high risk for not achieving a CR after reinduction chemotherapy, are referred to as having high-risk clinical features. This is in distinction to poor-risk cytogenetic features such as those specified by Eastern Cooperative Oncology and Southwest Oncology Group criteria. Primary induction failure was defined as being unable to achieve a CR after 1 cycle of induction chemotherapy. Duval score for refractory AML was calculated as previously described [5].

Treatment

AML induction, consolidation, and reinduction chemotherapy were performed according to available clinical trials or institutional standards. Preemptive alloHCT was defined as alloHCT performed as soon as possible after reinduction chemotherapy when AML was in a maximally reduced state. Preemptive alloHCT was prospectively planned for all patients with AML with high-risk features as defined above in Patient Population. Transplant conditioning regimens (myeloablative with busulfan/cyclophosphamide or etoposide/cyclophosphamide/total body irradiation or reduced intensity with fludarabine/melphalan or fludarabine/cyclophosphamide) were assigned based on baseline characteristics such as age, Karnofsky performance status, comorbidities, disease risk, and HLA matching. Acute graft-versus-host disease (GVHD) prophylaxis was assigned as tacrolimus only, tacrolimus/mycophenolate mofetil or a calcineurin inhibitor (tacrolimus or cyclosporine)/methotrexate ± other (methylprednisolone or mycophenolate mofetil) [6]. Tacrolimus doses were adjusted to maintain blood levels of 5 to 10 ng/dL during the first 100 days and then tapered off in the absence of GVHD by 6 months. Mycophenolate mofetil was discontinued at day +60 in the absence of GVHD.

Statistical Analysis

The Roswell Park Cancer Institute Institutional Review Board approved this retrospective analysis. The null hypothesis for the study stated that early p-alloHCT was not associated with a decrease in overall survival (OS) or increase in transplant-related mortality (TRM). The Pearson chi-square test or Fisher's exact text was used for univariate comparisons of categorical variables, and the ANOVA F-test was used for comparisons of continuous variables. OS was defined as the time from the date of blood and marrow transplant (BMT) (day 0) to the date of death due to any cause. Progression-free survival (PFS) was defined as the time from the date of BMT to first disease progression after BMT or death due to any cause. Patients who did not experience these events were censored at the time of last follow-up. Kaplan-Meier survival curves were constructed, and the difference was tested by the log-rank statistic. All statistical analyses were performed with SPSS version 21 (IBM, Armonk, NY) with 2-sided Type I error rate at .05.

Table 1
Reasons Patients Did Not Receive alloHCT

Reason	n (%)
Rapid disease progression	19 (23)
Patient refusal	15 (18)
Reinduction chemotherapy–related toxicity	14 (17)
Received an autologous BMT	11 (13)
Received transplant at another facility	7 (8)
Comorbidities	4 (5)
Stable disease	4 (5)
No donor	3 (4)
Financial issues	4 (5)
Psychosocial issues	2 (2)
Age	1 (1)

RESULTS

Patient and Disease Characteristics

Characteristics for 72 patients receiving alloHCT are presented in Table 2. Thirty of these 72 patients (42%) were identified as having high-risk clinical features predictive for not achieving CR after chemotherapy and thus were prospectively assigned to p-alloHCT after reinduction chemotherapy. Twenty-one of these patients with high-risk clinical features received early p-alloHCT. The other 9 received late p-alloHCT because of delays in going to transplant for logistical reasons. Restaging bone marrow biopsies performed after reinduction and immediately before transplant demonstrated hypoplasia (n = 11), refractory disease (n = 9), and CR (n = 1) in the 21 patients receiving early p-alloHCT. In the 9 patients receiving late p-alloHCT, restaging pretransplant bone marrow biopsies demonstrated hypoplasia (n = 2) and refractory disease (n = 7). Forty-two of the 72 patients (58%) who did not have high-risk clinical features achieved a CR with count recovery before alloHCT and received a standard alloHCT. Patient dispositions are shown in Figure 1.

The following analysis focuses on the 30 high-risk AML patients who received either early (n = 21) or late (n = 9) p-alloHCT. A higher proportion of the early versus late p-alloHCT group received 1 or more reinduction regimens (95% versus 66%). Gemtuzumab ozogamicin use was more frequent in the early versus late p-alloHCT group (57% versus 22%, respectively, $P = .09$). A lower proportion of patients in the early versus late p-alloHCT group had leukemia with adverse cytogenetics. Both early and late p-alloHCT groups had similar distributions in Duval score, age, presenting WBC counts, French-American-British classification, history of prior transplant, and bone marrow status before alloHCT. Compared with late p-alloHCT, a greater proportion of patients receiving early p-alloHCT had a Karnofsky performance status ≤80 (95% versus 67%) at the time of transplant. A greater proportion of early versus late p-alloHCT patients received reduced-intensity conditioning regimens before alloHCT (95% versus 78%). A higher proportion of patients in the early versus late p-alloHCT group received a graft from a <10/10 HLA matched unrelated donor