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Unrelated Donor Bone Marrow Transplantation Using a Chemotherapy-Only Preparative Regimen for Adults With High-Risk Acute Myelogenous Leukemia

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Limited data are available for adults undergoing unrelated donor (URD) BMT for AML using chemotherapy-only preparative regimens. Previous studies incorporated irradiation, included adults and children, and excluded secondary leukemia. Herein we report long-term outcomes for adults with poor-prognostic AML receiving a novel regimen of busulfan (16 mg/kg), cytarabine (8,000 mg/m^2), and cyclophosphamide (120 mg/kg) (BAC), followed by URD BMT. From June 1995 through October 2001, 45 adults were enrolled. Adverse features included unfavorable cytogenetics (49%), secondary AML (47%), leukemia at transplant (42%), and extramedullary disease (16%). At time of BMT, 23 were in remission (12 CR1) while 22 had leukemia. Four (9%) died early. Acute and chronic GVHD rates were 44 and 67%, respectively. Seventeen (38%) were disease-free 52 months post-BMT; 13 were leukemia-free (eight CR1) at transplant. Eleven relapsed. Three-year DFS and OS were 42 and 46%, respectively. DFS and OS were longer, and relapses less, for those in CR at time of BMT. Secondary leukemia, cytogenetics, cell dose, and GVHD did not influence outcome. In poor-risk AML, BAC provided cytoreduction comparable to reported TBI-containing regimens, when administered for URD BMT. With decreasing treatment-related mortality, it is justified to proceed early to URD BMT for patients with poor prognostic features. Am. J. Hematol. 82:6–14, 2007. © 2006 Wiley-Liss, Inc.

Key words: unrelated donor BMT; AML; high-close chemotherapy; BAC preparative regimen

INTRODUCTION

Allogeneic bone marrow transplantation (BMT) from related donors is an established and effective treatment for many adults with acute myelogeneous leukemia (AML). For those patients without a matched related donor, transplantation using a HLA-matched unrelated donor (URD) is a viable option for two-thirds of patients requesting a donor through the National Marrow Donor Program (NMDP). To date, most of the published data for patients with AML requiring an URD BMT have been derived from relatively small pilot studies demonstrating feasibility in terms of engraftment and toxicity [1–6]. The majority of studies incorporated a total body irradiation (TBI)-containing preparative regimen, included both adults and children as subjects, often excluded secondary leukemia, and were published with short follow-up. Despite aggressive therapy, relapse remains a major cause of treatment failure for those undergoing transplantation with active disease.

In 1983, Santos et al. developed a chemotherapy-only preparative regimen of busulfan and cyclophosphamide (200 mg/kg) (BU/CY-4), and demonstrated efficacy comparable to TBI-containing regimens for patients with AML [7]. In an effort to ameliorate toxicities seen with BU/CY-4, Tutschka et al. significantly reduced the dosage of cyclophosphamide

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(120 mg/kg) without compromising treatment outcome (BU/CY-2) [8]. In the early 1990s, four randomized trials compared BU/CY with cyclophosphamide and TBI (CY/TBI) in related allogeneic transplantation for myeloid (all trials) and lymphoid (one trial) malignancies [9–12]. Two trials demonstrated improved disease-free survival (DFS) with CY/TBI [9,10], while the other two did not [11,12]. A meta-analysis of these four trials, with follow-up ranging from 24 to 42 months, concluded that CY/TBI provided a nonsignificant trend toward improved disease-free and overall survival (OS) [13]. With extended follow-up of the 172 patients with AML participating in these trials, 10-year DFS rates were 57% (95% CI, 44–70%) and 47% (95% CI, 36–58%) with CY/TBI and BU/CY, respectively ($P = 0.05$) [14].

Beginning in 1995, we chose to evaluate a novel chemotherapy-only preparative regimen for adults with primary and secondary AML undergoing URD BMT. The BAC regimen, previously described by our group in allogeneic related BMT, incorporates high-dose cytarabine with BU/CY-2 [15]. Resistance to standard dose cytarabine can be multifactorial, including decreased membrane transport, increased catabolism of the parent compound, and decreased formation of phosphorylated derivatives [16–18]. High-dose cytarabine can overcome resistance by altering drug transport into cells [16]. As cytarabine is one of the most effective agents used for treatment of AML, the addition of high-dose cytarabine to BU/CY might enhance cytoreduction with manageable regimen-related toxicity. Herein we demonstrate the favorable activity of BAC, comparable to reported TBI-containing regimens, in adults with primary and secondary AML presenting with poor prognostic features.

MATERIALS AND METHODS

Patient Selection

Adults with high-risk AML (de novo or secondary) and RAEB-t undergoing URD BMT were eligible. Patients in first complete remission (CR1) were required to have at least one poor-risk feature: unfavorable cytogenetics, secondary AML, or failure to attain remission with first induction chemotherapy. Karyotype abnormalities were categorized as favorable [t(15;17), t(8;21), or inv(16)], intermediate (normal karyotype or a single abnormality not classified as unfavorable), or unfavorable [del(5) or del(7), abnormalities of chromosome 9 or 11, or multiple clonal abnormalities] [19]. Eligibility requirements included adequate organ function and good performance scores. All patients gave written informed consent. The study was approved by the IRB at the University of Michigan.

Preparative Regimen

The BAC regimen included busulfan (4 mg/kg po in divided doses daily on days −9 through −6; total dose 16 mg/kg), cytarabine (2,000 mg/m^2 twice daily by 2-hr infusion on days −5 and −4; total dose 8,000 mg/m^2), and cyclophosphamide (60 mg/kg once daily by 2-hr infusion on days −3 and −2; total dose 120 mg/kg) [15]. Phenytoin was given to prevent busulfan-induced seizures and Mesna administered to avoid hemorrhagic cystitis (100% of cyclophosphamide dose). Intrathecal cytarabine (30 mg/m^2) was given for CNS prophylaxis pre-transplant and on days 60 and 90 if the platelet count was adequate.

Donor Bone Marrow Harvest or Leukapheresis, Recipient Transplantation

Allogeneic cells were harvested from HLA A, B, and DR identical or one-antigen mismatched donors. Donors were matched at the antigen level at the A and B loci and the allele level at DR. A marrow harvest target of 4.0×10^8 MNC/kg was collected and administered without cryopreservation. One patient received G-CSF primed PBSC. Allogeneic cells were infused 48 hr after completing chemotherapy (day 0). G-CSF (5 μg/kg/day sq) was begun on day 6, and continued until an absolute neutrophil count (ANC) $\geq$ 1,000/μl was achieved.

Graft-versus-Host Disease Prophylaxis, Diagnosis, and Treatment

Patients received tacrolimus (0.03 mg/kg/day by lean body weight) beginning day −1, with doses adjusted to maintain blood levels of 10–20 ng/ml. Dose reductions occurred if toxicity was observed. Beginning day 56, tacrolimus was tapered 20% every 4 weeks and discontinued on day 180 if GVHD was not observed. Methotrexate was given on days 1, 3, 6, and 11 post-transplant. Short-course methotrexate (15 mg/m^2 on day 1, 10 mg/m^2 on days 3, 6, and 11) was administered to the first nine patients, after which minidose methotrexate (each dose 5 mg/m^2) was given to decrease mucositis. The decision to administer methotrexate was determined by the severity of mucositis, the amount of weight gain, the presence of third-spacing, and renal and liver functions on the day the drug was due.

Acute and chronic GVHD were graded by consensus criteria [20,21]. Acute GVHD was treated initially with methylprednisolone (2 mg/kg/day) and tacrolimus. Chronic GVHD was evaluated in those

surviving at least 100 days, and treated as clinically indicated.

Definitions and Statistical Analysis

Hematopoietic recovery was measured from day 0 to the first of three consecutive measurements of an ANC $\geq$ 500/μl and platelets $\geq$ 20,000/μl, independent of transfusions. Marrow and blood evaluations to determine disease and chimerism status were performed on day 30 and as clinically warranted.

Descriptive statistics were reported as frequencies or medians. OS and DFS were defined from day of transplant to day of death or disease progression, respectively. OS and DFS were estimated by the Kaplan-Meier product limit method. Cumulative incidences of acute GVHD, chronic GVHD, and relapse were determined using the methodology of Gooley [22], with variance estimates based upon the methodology of Pepe [23]. The log-rank test compared differences between patient subgroups. Cox regression analyses were performed to determine univariate associations of patient variables (secondary leukemia, unfavorable cytogenetics, disease status at BMT, cell doses, HLA match, acute or chronic GVHD) to disease outcomes (DFS, OS, relapse). Acute and chronic GVHD were modeled as time-varying covariates. P values were two-sided, and $P < 0.05$ was significant.

RESULTS

Patient Characteristics (Table I)

From June 1995 through October 2001, 45 patients entered study. The median age at BMT was 44 years (range, 19–58). Twenty-one (47%) patients had secondary AML: 12 with pre-existing myelodysplasia (MDS), 5 received prior chemoradiotherapy, and 4 others had predisposing disorders (Kostman's syndrome, aplastic anemia, myeloproliferative disease, renal transplant). Of 8 patients with RAEB-t, 7 had transformed to acute leukemia while 1 had 20% blasts prior to BMT. Other poor risk features included unfavorable cytogenetics (22 patients), failure to attain remission with first induction (16 patients), and extramedullary disease (7 patients). Of the 12 patients in CR1, 10 had unfavorable cytogenetics, 9 had secondary AML, and 3 required more than one induction to achieve CR.

Twenty-three patients achieved remission (12 CR1, 10 CR2, 1 CR3) to induction chemotherapy, 16 had refractory disease (8 primary induction failure, 8 refractory relapse), and three were untreated at first relapse. Three did not receive any induction (MDS, aplastic anemia, renal transplant). The median time from diagnosis to BMT was 8 months (range, 2–54) for all patients. For those in CR1, the median time to transplant was 6 months.

TABLE I. Patient, Donor, and Disease Characteristics

Variable	Number
Median age at BMT	
Recipient	44 years (range, 19–58)
Donor	36 years (range, 21–54)
Gender of recipients	27 males/18 females
De novo AML	24 (53%)
Secondary AML	21 (47%)
Primary myelodysplasia	12
Chemoradiotherapy-induced	5
Kostman's syndrome/aplastic anemia	2
Myeloproliferative disorder	1
Renal transplant recipient	1
Cytogenetics	
Favorable	3
Intermediate	20
Unfavorable/complex	22 (49%)
Extramedullary sites	7 patients (16%)
CNS	3
Skin	3
Other sites	4
Response to induction	
Remission	26 (58%)
Persistent leukemia	16 (36%)
No induction	3
Disease status at transplant	
CR1	12 (26%)
CR2/CR3	10/1
Active leukemia	22 (48%)
Never treated	3
First relapse	3
Primary induction failure	8
Refractory relapse	8
HLA match	
6/6	36
5/6	9 (20%)
Stem cell source	
Bone marrow	44
PBSC	1
Median cell dose	
MNC (10^8/kg)	2.4 (range, 1.1–4.4)
CD34 (10^6/kg)	3.5 (range, 1.3–10.2)

Engraftment and Toxicity

Thirty-six (80%) patients received cells from a 6/6 HLA-matched donor and nine from a 5/6 mismatched donor. The median mononuclear and CD34 cell doses infused were 2.4×10^8/kg (range, 1.1–4.4) and 3.5×10^6/kg (range, 1.3–10.2), respectively.

There were four early (<day 30) treatment-related deaths. Three patients died from GVHD (on days 58, 68, and 71) before platelet recovery and two others had primary graft failure (one 5/6 HLA match). Excluding those patients, the median days

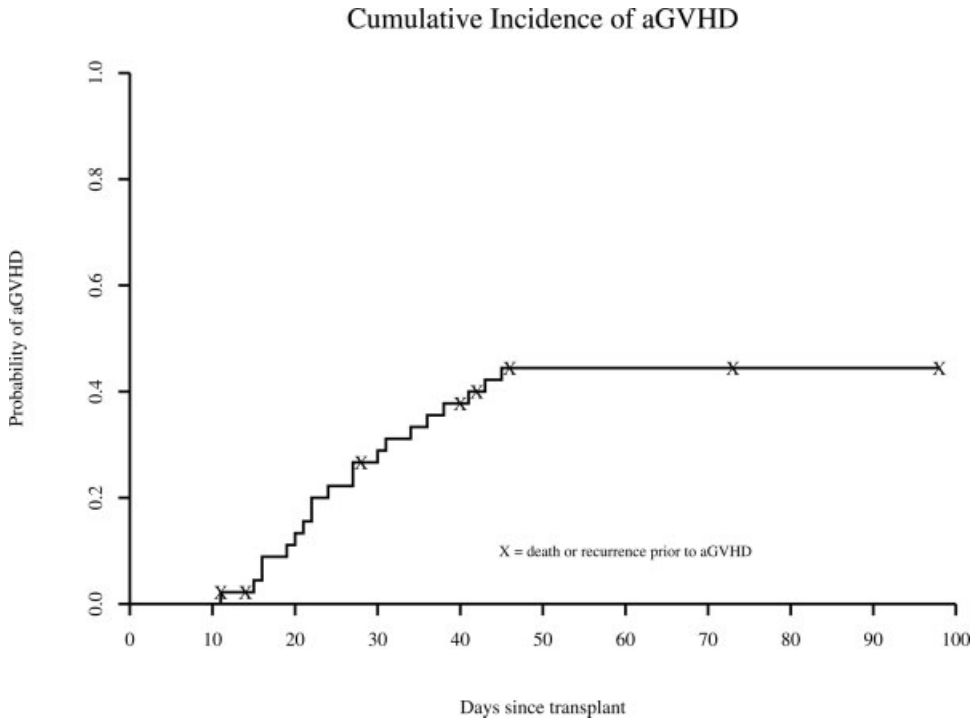

Fig. 1. (aGVHD): The cumulative incidence of grades II–IV acute GVHD was 44% (95% CI, 31–60%).

to an ANC > 500/μl and platelets > 20,000/μl were 16 (range, 11–25) and 24 (range, 13–132), respectively.

Toxicities seen within 100 days post-transplant included (No. of patients): moderate/severe mucositis (32), pneumonia/pneumonitis (11), hemorrhagic cystitis (10), hepatic venoocclusive disease (5), and renal insufficiency requiring hemodialysis (3). Infections during that period included (no. of patients): bacteremia (23), c. difficile (5), CMV viremia (5), fungal infections (4), varicella zoster (2), and atypical mycobacteria (2).

Acute and Chronic GVHD

Twenty patients developed grades II-IV acute GVHD and 10 grades III-IV acute GVHD. The cumulative incidences of grades II-IV and III-IV acute GVHD were 44% (95% CI, 31–60%) and 22% (95% CI, 11–42%), respectively (see Fig. 1). Nine patients received a mismatched BMT; 2 died early of toxicity and 1 never engrafted. Of the remaining 6 mismatched transplant patients, 4 developed acute GVHD with 3 subsequently dying from grade IV GVHD.

Thirty-one patients were alive without relapse at day 100. Twenty patients developed chronic GVHD (3 limited; 17 extensive), for a 1-year cumulative incidence of 67% (95% CI, 51–81%) (see Fig. 2). Of the 17 patients presently alive and disease-free, 12 had experienced GVHD (5 acute and 12 chronic GVHD).

Survival and Relapse

Four (9%) patients died before day 30 of toxicity, thus 41 were evaluable for response. Of 19 patients undergoing BMT with active leukemia (excluding three early deaths), 17 entered CR, 1 had primary graft failure without leukemia, and 1 had persistent blasts at day 30 marrow evaluation. The median DFS and OS for the whole group were 389 and 535 days, respectively. DFS at 3 and 5 years were 42% (95% CI, 30–59%) and 35% (95% CI, 22–54%), respectively. OS at 3 and 5 years were 46% (95% CI, 34–63%) and 35% (95% CI, 21–55%), respectively (see Fig. 3).

Seventeen (38%) patients are alive and disease-free at a median follow-up of 52 months (range, 28–101) post-transplant. Disease status at BMT for the survivors included 8 in CR1, 5 in CR2, and 4 with leukemia (2 with refractory disease). Ten had unfavorable cytogenetics at initial diagnosis, 8 had secondary leukemia, 5 had failed first induction therapy, 2 developed CNS relapse before BMT, and 1 received a HLA-mismatched transplant.

Eleven relapses appeared at a median of 163 days (range, 40–521) post-transplant. Three relapses occurred more than 1 year after BMT (at 13, 16, and

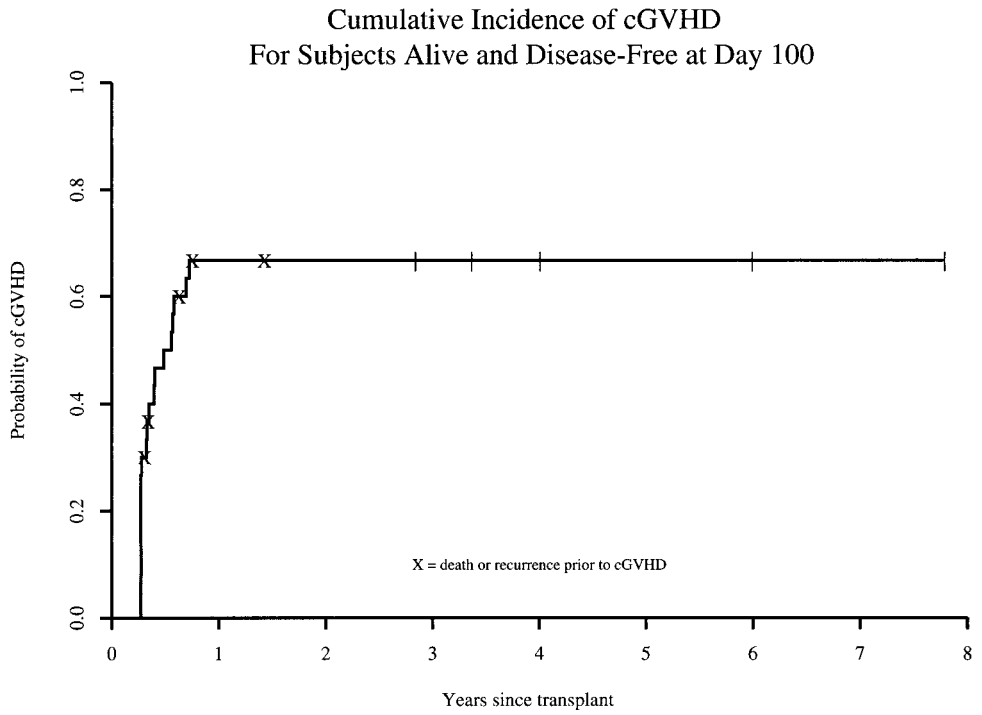

Fig. 2. (cGVHD): The 1-year cumulative incidence of chronic GVHD was 67% (95% CI, 51–81%).

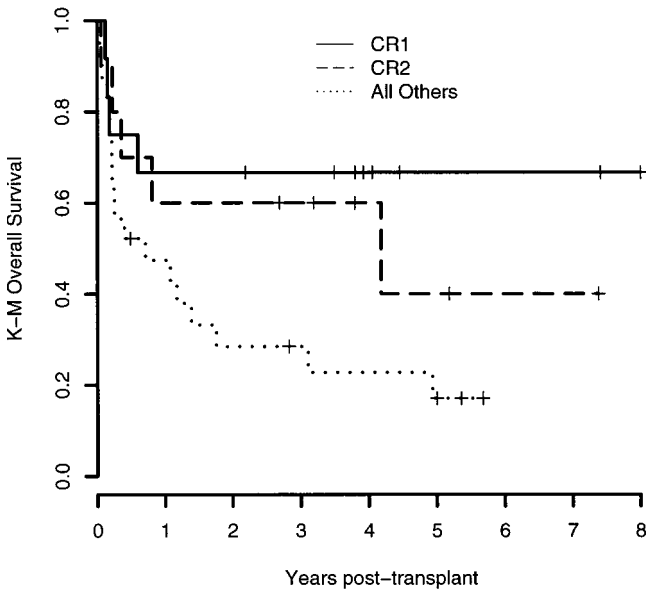

Fig. 3. (Plot C): The 3-year overall survival for the whole group was 46% (95% CI, 34–63%). OS was significantly longer for those in CR1/CR2 at time of BMT.

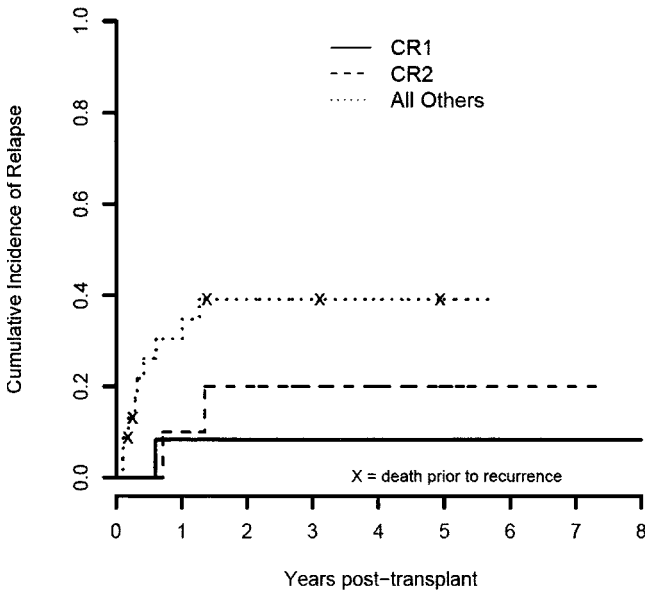

Fig. 4. (Rel Plot C): The 3-year cumulative incidence of relapse for the whole group was 27%. The relapse rate was significantly lower for those in CR1/CR2 at time of BMT.

17 months). The 3-year cumulative incidence of relapse was estimated at 27% for the whole group (see Fig. 4). All died subsequently from disease progression.

Twenty-eight (62%) patients have died, most from disease progression (11 patients) (Table II). The rest suffered either regimen-related complications (8 patients), GVHD (8 patients), or relapse of a previous malignancy (one sarcoma). All but one of nine patients undergoing mismatched transplants have died: 3 from toxicities, 3 from acute GVHD, and 2 from relapsed AML.

TABLE II. Cause of Death (*N* = 28)

Variable	Number
Relapsed AML	11
GVHD	8
Regimen-related toxicity	
Infection	5
Graft failure	1
Pulmonary failure	1
Cardiomyopathy	1
Relapse of primary cancer	1

Univariate Analysis

DFS and OS were significantly longer for those in CR1/CR2 ($P = 0.01$ and 0.02, respectively), and relapse rate lower ($P = 0.02$), when compared to those with leukemia at BMT. Survival was also enhanced for those having a HLA-compatible donor ($P = 0.01$). There was a strong trend toward improved OS with those in CR1 versus all others ($P = 0.08$). Secondary leukemia, unfavorable cytogenetics, cell dose infused, and acute or chronic GVHD did not influence outcome.

DISCUSSION

There is a paucity of data reported for adults undergoing URD BMT for primary and secondary AML using chemotherapy-alone preparative regimens. In this study, 45 adults received BAC with URD BMT with the hope that adding cytarabine might enhance cytoreduction with manageable toxicity. Poor-prognostic features included: unfavorable cytogenetics (49%), secondary AML (47%), active leukemia at BMT (42%), lack of remission with first induction (35%), and extramedullary disease (16%). All 12 patients in CR1 at BMT demonstrated at least one adverse feature, and eight had at least two. The cumulative incidences of acute and chronic GVHD were 44 and 67%, respectively. Seventeen (38%) patients are alive and well at a median follow-up of 52 months post-BMT; 13 were leukemia-free (8 CR1, 5 CR2) at BMT. Three-year DFS and OS were 42 and 46%, respectively. DFS and OS were significantly longer for those in CR1/CR2, and relapse rate lower, when compared to those with leukemia at BMT. Survival was also significantly better for those having a 6/6 HLA-matched donor. Secondary leukemia, unfavorable cytogenetics, cell dose infused, and GVHD did not influence outcome. There are a number of observations made during this study, and in a review of the literature, that are worthy of comment.

First, the chemotherapy-only regimen BAC appears equally efficacious to CY/TBI when examined by disease status at time of URD transplantation. Two groups (NMDP and University of Washington, Seattle) have the largest outcomes data, primarily employing CY/TBI as a preparative regimen. As of June 2001, outcomes were available for 1,620 patients undergoing an URD BMT for AML (302 patients in CR1, 398 in CR2, and 920 in $\geq$CR3 or relapse) through the NMDP (www.marrow.org). Approximately 81% received a TBI-containing regimen. Five-year survivals for those in CR1, CR2, or with advanced disease were 32, 29, and 11%, respectively. These data did not differentiate between primary and secondary AML. A retrospective comparison of TBI-based or chemotherapy-only preparative regimens given to 5,699 patients (1,342 with AML) undergoing URD transplantation revealed similar relapse rates, non-relapse mortality, and survival [24]. The Seattle group treated 161 primary AML patients (median age 30) with CY/TBI (96%) and URD BMT [5,6]. Five-year DFS was 50% for patients in CR1, 28% for CR2, 19% for primary induction failure, and 7% for relapse. Patients in CR receiving marrow cell doses above the median (3.5×10^8 MNC/kg) had the best DFS. Although our study did not demonstrate an effect of higher cell doses, CR status at BMT did impact survival, with $>60\%$ of those in CR1 disease-free 4 years later.

Second, unfavorable cytogenetics may lose prognostic significance if associated with CR status at time of URD transplantation. At least 50% of adults with de novo AML present with abnormal karyotypes, which can be classified into three risk groups predictive for response and survival after conventional chemotherapy: favorable (CR 88%, OS 55%), intermediate (CR 67%, OS 24%), and adverse (CR 32%, OS 5%) [25]. The Medical Research Council AML 10 trial confirmed this risk stratification in children and adults (aged $\leq$55 years) presenting with secondary as well as de novo AML [26]. While such prognostic indicators influence post-remission therapy, it remains controversial whether allogeneic transplantation can overcome the poor prognosis associated with unfavorable cytogenetics. For patients with AML in CR1 presenting with adverse cytogenetics, some trials have shown improved outcome for those undergoing allogeneic BMT from related donors [27–29], while others have not [30,31]. Data assessing karyotype and outcome are lacking for URD BMT, in part due to reluctance to proceed to transplant in CR1 secondary to expected high treatment-related mortality. In the largest study available, cytogenetics did not influence outcome for 161 primary AML patients undergoing

URD BMT in Seattle [6]. Of the 22 patients in our study with unfavorable cytogenetics, 8 of 12 transplanted in CR remain leukemia-free, compared with only 2 of 10 with active leukemia. Three relapses were observed and all had leukemia at BMT.

Third, URD transplantation may be an important therapeutic modality for those with poor-risk features in CR1. Four recent prospective trials randomized patients in CR1 to allogeneic BMT if a HLA-related donor was available, or to either autologous BMT or intensive chemotherapy [32–35]. Using an intention-to-treat analysis, these trials demonstrated a lower relapse rate for either transplant modality (with the lowest relapses after allogeneic transplant) when compared to chemotherapy alone. OS was not improved after allogeneic BMT however, due to increased treatment-related mortality, salvage with BMT after relapse from chemotherapy, and a high failure to comply with the randomized treatment, such that only a minority of patients actually received BMT. In the two trials for which karyotypes were available [26,27], cytogenetic risk was prognostic for outcome, however only the US intergroup trial showed a survival benefit for patients with adverse cytogenetics undergoing allogeneic BMT [27]. The EORTC/GIMEMA AML-10 trial randomized patients in CR1 to either allogeneic stem cell transplant (SCT) if a sibling donor was available or to autologous SCT if no donor was found [29]. Both relapse rate and DFS were significantly better for patients undergoing allogeneic SCT. When assessed by cytogenetic risk, DFS was similar for those with good/intermediate risk cytogenetics, but markedly improved (43.4% vs. 18.4%) for those with adverse karyotype undergoing allogeneic SCT.

While related donor transplantation is justified for CR1 patients with adverse prognostic features, the appropriate post-remission strategy for patients without a family donor remains undefined. There are no large prospective trials evaluating autologous, unrelated donor, and/or cord blood stem cells as alternative sources for this subset of patients. Patients with poor-risk cytogenetics comprise a very small subset of patients undergoing autologous transplantation due to the difficulty achieving and maintaining remission, as well as the inadequacy of stem cell harvests secondary to underlying myelodysplasia. Two recent analyses of registry data compared outcomes using URD BMT with cord blood transplantation for adults with leukemia [36,37]. In both series, cord blood recipients were younger, had more advanced disease, and experienced slower hematopoietic recovery due to lower cell doses. Although both studies found no differences in risk of relapse, neither recommended cord blood over HLA-matched marrow in adults. With 1-year treatment-related mortality decreasing (29% during the years 1999–2003, NMDP data) and more precise molecular HLA typing available, URD transplantation done early in the disease course becomes a feasible option. Unlike CR2 patients for whom survival is similar using unrelated or sibling donors, there remains a 10–20% decrement in survival for CR1 patients undergoing URD when compared to sibling BMT. In our small cohort of 12 CR1 patients receiving BAC, however, no relapses were observed and eight remain alive and well a median of 52 months post-BMT.

Finally, URD BMT is not able to overcome the dismal prognosis associated with leukemia refractory to induction therapy. Those patients with overt relapse at time of BMT do poorly, with only $\sim 10\%$ long-term survival noted despite transplantation. Relapse remains the predominant cause of treatment failure, but pronounced treatment-related toxicities in patients with active disease contribute to the mortality observed. Likewise, the Seattle group could not discern an advantage for URD BMT in early "untreated" relapse when compared with treatment-refractory relapse (5-year DFS 12% vs. 5%, $P = 0.2$) [5]. Patients with $> 30\%$ marrow blasts or any peripheral blood blasts experienced mortality and relapse that approached 100%. New therapeutic modalities are desperately needed for this patient population.

The role of reduced intensity conditioning regimens for patients with AML undergoing URD transplantation is at present undefined. These regimens offer the potential for reduced regimen-related toxicity, while depending to a greater extent on immunologic-mediated cell killing for curative potential. De Lima et al. performed a retrospective analysis comparing a truly nonmyeloablative regimen with a more myelosuppressive treatment in AML and MDS patients undergoing allogeneic transplantation [38]. The more myelosuppressive regimen was associated with higher treatment-related mortality, but also a significantly lower incidence of relapse and relapse-related mortality. Survival was improved with either regimen for patients in complete remission at time of transplantation.

CONCLUSIONS

In summary, BAC is a highly effective preparative regimen, comparable to Cy/TBI, for patients with AML undergoing URD BMT. Disease status at BMT was most prognostic for survival, with patients in CR faring significantly better than those with active leukemia. While secondary leukemia, adverse

cytogenetics, higher cell doses, and GVHD did not influence outcome in our study, one or more such variables may achieve importance with greater patient numbers. Perhaps the most important aspect of this study was the favorable results observed for patients transplanted in CR1. With decreasing treatment-related mortality and the ability of patients to withstand toxicities better with minimal residual disease, it is justified to proceed to URD BMT early for patients with adverse prognostic factors. Until improvement in the prevention and treatment of GVHD becomes a reality, the role of URD BMT for intermediate-risk AML requires exploration through prospective clinical trials.

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