Research paper

haematologica 2002; 87:52-58
http://www.haematologica.it/2002_01/052.htm

Standard versus alternative myeloablative conditioning regimens in allogeneic hematopoietic stem cell transplantation for high-risk acute leukemia

ANDREA MENGARELLI, ANNAPAOLA IORI, CESARE GUGLIELMI, ATELDA ROMANO, RAFFAELLA CERRETTI, CONCETTA TORROMEO, ALESSANDRA MICOZZI, SUSANNA FENU, LUCA LAURENTI, VITTORIO DONATO,* LIDIA DE FELICE, WILLIAM ARCESE

Dipartimento di Biotecnologie Cellulari ed Ematologia, Università "La Sapienza", Roma, Italia; *Istituto di Radiologia e Radioterapia, Università "La Sapienza", Rome, Italy

Correspondence: William Arcese, MD, Cattedra di Ematologia, Via Benevento 6, 00161, Rome, Italy.
Phone: international +39.06.857951. Fax: international +39.06.44241984. E-mail:arcese@bce.med.uniroma1.it

Background and Objectives. To analyze the results of standard versus alternative myeloablative conditioning regimens in allogeneic hematopoietic stem cell transplantation for high-risk acute leukemia.

Design and Methods. From October 1986 to February 2000, 104 consecutive patients (male: n = 63; median age: 21, range 1.3-44.2 years) with high-risk acute leukemia underwent a non-T-cell depleted graft from an HLA-identical sibling following a standard or alternative myeloablative conditioning regimen. Sixty patients were affected by acute lymphoblastic leukemia (ALL) and 44 by acute myeloid leukemia (AML); the phase at transplant was ≥ 2nd complete remission (CR) in 76, untreated 1st relapse with < 20% blasts in 11, refractory leukemia or overt resistant relapse in 17. Pre-transplant regimens consisting of either 12 Gy fractionated total body irradiation (TBI) or 16 mg/kg busulphan (BU) combined with cyclophosphamide (CY) were defined *standard* (n = 38), whereas all other myeloablative regimens (TBI plus 60 mg/kg etoposide and three-drug combinations) were considered *alternative* (n = 66).

Results. No significant differences in terms of baseline characteristics, incidence and severity of either acute or chronic graft-versus-host disease (GVHD) were observed between the two groups, but a significantly higher proportion of patients prepared with an alternative regimen were not evaluable for chronic GVHD (36% vs 16%) (p = 0.026). Sixty-six patients died, 38 of relapse, 26 of transplant-related mortality (TRM) and 2 of other causes. Thirty-eight patients are still alive with a follow-up ranging from 0.7 to 13.8 years (median, 7.1 years); only 1 of 39 patients who relapsed after transplant is alive in CR at 5.7 years from relapse. At the median follow-up, the actuarial probabilities of overall survival, relapse and TRM for patients conditioned with standard and alternative regimens are respectively 52% vs 25% (95% CI, 36-68% vs 13-37%; p = 0.0163), 34% vs 58% (95% CI, 18-51% vs 43-73%; p = 0.0377) and 25% vs 32% (95% CI, 9-40% vs 19-44%; p = ns). After adjustment for diagnosis, age, period, leukemia phase, duration of 1st CR, GVHD prophylaxis and donor-recipient sex combination, the multivariate analysis showed that alternative regimens are associated with a significantly worse survival (hazard ratio 2.31; p = 0.0071) and relapse rate (hazard ratio 2.75; p = 0.0187).

Interpretation and Conclusions. From this retrospective analysis we can conclude that the alternative myeloablative conditioning regimens we used did not improve the outcome of patients transplanted for high-risk acute leukemia.

Key words: alternative myeloablative conditioning, high-risk acute leukemia, allogeneic stem cell transplantation.

For patients with high-risk acute leukemia undergoing an allogeneic hematopoietic stem cell transplant (SCT) from an HLA-identical sibling, a major obstacle to success is represented by the relapse of the underlying disease. Following the Seattle regimen of total body irradiation (TBI) and cyclophosphamide (CY) the relapse rate (RR) ranges from 25 to 50% for patients transplanted in 2nd complete remission (CR) and is more than 50% for those transplanted in a more advanced phase of the disease.[1-4] TBI or busulphan (BU) combined with

CY have long represented the classical conditioning regimens used worldwide to prepare patients to receive an allogeneic SCT.[5-6] However, from the EBMT retrospective analysis no substantial difference was found in the outcome of patients with *intermediate* acute leukemia undergoing an allogeneic bone marrow transplant after TBI or BU-based conditioning.[7] Although some non-randomized studies on the use of an intensified conditioning have reported an improving outcome for high-risk patients,[8-10] the search for regimens alternative to the standard (TBI-CY or BU-CY) aiming at reducing the RR without increasing transplant-related mortality (TRM) has proven to be difficult.[11] Only one randomized trial has compared the classical BU-CY combination to an alternative regimen consisting of fractionated TBI followed by high-dose etoposide (VP16) in patients with advanced leukemia.[12] When adjusted for age, no significant difference in outcome was found between the two treatment groups. Considering the current debate on the use of non-myeloablative conditioning regimens it is important to keep in mind that, as compared to chronic myeloid leukemia (CML), the graft-versus-leukemia (GVL) effects in acute myeloid leukemia (AML) are less pronounced and even less in acute lymphoid leukemia (ALL).[13-14]Therefore, myeloablative regimens should, in principle, be more appropriate in preparing patients with acute leukemia, particularly if transplanted in an advanced phase of the disease. However, in this setting, it remains an open question whether or not the use of more intensive regimens alternative to the standard ones is preferable. We report here the results obtained in our institute retrospectively comparing standard versus alternative myeloablative conditioning regimens in allogeneic hematopoietic stem cell transplants for high-risk acute leukemia over a period of several years.

Design and Methods

Patients

From October 1986 to February 2000, 104 consecutive patients with high-risk acute leukemia received a non-T-cell depleted graft from an HLA-identical sibling. Part of this patient series has been described previously.[15] Of the 104 patients, 60 were affected by ALL and 44 by AML; the phase at transplant was ≥ 2nd CR in 76 patients, untreated 1st relapse with < 20% blasts in 11, refractory leukemia or overt resistant relapse in 17. Sixty-three patients were male. The median age was 21 years (range, 1.3-44.2 years). The stem cell source was bone marrow in 98 cases and peripheral blood in 6.

Conditioning regimens

The following regimens used to prepare patients for SCT were considered *standard*:

- TBI-CY2 (n = 7): fractionated 12 Gy TBI over 3 days (2 Gy twice daily) followed by CY 120 mg/kg over 2 days;
- BU-CY2 (n = 24): BU 16 mg/kg over 4 days followed by CY 120 mg/Kg over 2 days;
- BU-CY4 (n = 7): BU 16 mg/kg over 4 days followed by CY 200 mg/Kg over 4 days.

The following regimens were considered *alternative*:

- VP16-TBI (n = 43): etoposide 60 mg/kg total dose, administered by continuous i.v. infusion over 3 days, followed by fractionated 12 Gy TBI over 3 days;
- Three-drug regimens (n = 23): fractionated TBI-CY or BU-CY combined with idarubicin 42 mg/m^2 over 2 days (n = 17) or VP16 20 mg/kg (n = 4) or Ara-C 2 g/m^2 twice daily over 2 days (n = 2).

Graft-versus-host disease prophylaxis

All patients received cyclosporine (CsA). A short-course of methotrexate (MTX) was given to 41 patients. Low doses of 6-methylprednisolone (PDN) were added to CsA and CsA-MTX in 9 and 8 patients, respectively. Acute and chronic graft-versus-host disease (GVHD) was diagnosed and graded according to the established criteria.[16-17] All engrafted patients surviving with a full donor chimerism at least 100 days after transplant were considered evaluable for chronic GVHD.

Endpoints and statistical methods

The primary endpoint was overall survival (OS), defined as the time from the SCT to death from any cause or to the study closure date of November 1st, 2000. Probabilities of TRM and relapse were also considered. Time to transplant-related death was measured from the date of SCT to the date of death in CR, censoring relapses and two cases of death in CR caused by a second tumor and a cardiac attack occurring 8.5 and 3.3 years after SCT, respectively. Time to relapse was measured from the date of SCT to the date of relapse, censoring deaths in CR. Baseline patient characteristics were compared using the χ^2 test for categorical variables and the Mann-Whitney test for continuous ones. The actuarial probabilities of survival, relapse and TRM were estimated by the method of Kaplan and Meier.[18] Comparison of survival curves for selected subgroups was performed by the log-rank (Mantel-Cox) test.[19] The following features were studied: type of acute

Table 1. Patients' characteristics.

Conditioning regimen	*Standard*	*Alternative*	*p value*
No. of patients	38	66	
Diagnosis			ns
ALL	20	40	
AML	18	26	
Sex			ns
Male	21	42	
Female	17	24	
Age (years)			ns
Median (range)	20 (1.3-38.8)	22.9 (3-44.2)	
Year of transplant			< 0.0001
1986-May 1993	30	22	
June 1993-2000	8	44	
Leukemia phase			ns
Intermediate	34	53	
CR ≥ 2 (≥ 3)	*29 (9)*	*47 (9)*	
Untreated 1st relapse	5	6	
Advanced	4	13	
Primary refractory	*1*	*6*	
Resistant 1st relapse	*1*	*4*	
Relapse ≥ 22	*3*		
Duration of 1st CR (months)			ns
Median (range)	13.5 (0.4-68)	15.6 (0.6-118.9)	
Not applicable (no.)	1	6	
Time from last relapse to last CR (days)			ns
Median (range)	39 (25-232)	34 (20-254)	
Not applicable (no.)	9	19	
Time from last CR to transplant (days)			ns
Median (range)	71 (12-268)	84 (7-286)	
Not applicable (no.)	9	19	
Stem cell source			ns
BM	38	60	
PB	0	6	
GVHD prophylaxis			ns
CsA±PDN	24	39	
CsA+MTX±PDN	14	27	

leukemia (AML vs ALL), patients' sex (male vs female), patients' age (< vs > median age), period of SCT (< vs > median date), disease phase at time of transplant (intermediate vs advanced), duration of 1st CR (< vs > median time), conditioning regimen (standard vs alternative), GVHD prophylaxis (CsA±PDN vs CsA+MTX±PDN), sex combination (donor female/recipient male vs other), acute GVHD (0 vs 1-2 vs 3-4), chronic GVHD (no vs yes). A p value < 0.05 was considered statistically significant. A Cox proportional hazards regression single step model was set up.[20] The relative risks of death, relapse and TRM using standard conditioning regimens as the reference group were calculated after adjustment for diagnosis, age, period, leukemia phase at time of SCT, duration of 1st CR, GVHD prophylaxis and donor-recipient sex combination. Ninety-five percent confidence intervals (CI) are reported for the main summary statistics.

Table 2. Patients' outcome.

	Regimen		
	Standard	*Alternative*	*p value*
No. of patients	38	66	
Acute GVHD incidence			ns*
Grade 0-1	22 (58%)	35 (53%)	
Grade 2-4	16 (42%)	31 (47%)	
Chronic GVHD			
No. of evaluable patients	32 (84%)	42 (64%)	0.026*
Rate	41% (±9.7%)	44% (±9.7%)	ns§
No. of relapsing patients	11	28	
Median (range) time to relapse, yrs	0.5 (0.2-2.5)	0.4 (0.1-5)	
Relapses < 100 days	2 (18%)	11 (39%)	
No. of deaths	20	46	
Causes of death			
Leukemia relapse	11	27	
Transplant-related	8	18	
Other	1	1	
Alive in CR	18	20	
Median (range) follow-up, yrs	9.4 (1.3-12.7)	5.5 (0.7-13.8)	

**Calculated using the χ^2 test; §actuarial probabilities (±standard error) of chronic GVHD were compared using the log-rank test.*

Results

Patients' characteristics

The characteristics of the patients and their diseases are summarized in Table 1. The only significant difference between the two groups consisted of a progressively more frequent use of alternative conditioning regimens over the years.

Outcomes

Table 2 details the patients' outcome. No difference in terms of acute and chronic GVHD incidence and severity was observed between the two treatment groups, but a significantly lower proportion of patients prepared with an alternative regimen was evaluable for chronic GVHD (64% vs 84%) (p = 0.026). This difference was mainly due to the higher number of early relapses and regimen-related deaths occurring in patients conditioned with an alternative regimen. Thirty-nine relapses occurred at a median of 0.4 years after SCT (range, 0.1-5 years) of which 13 were observed within 100 days; it is noteworthy that only 2 of these 13 patients (15%)

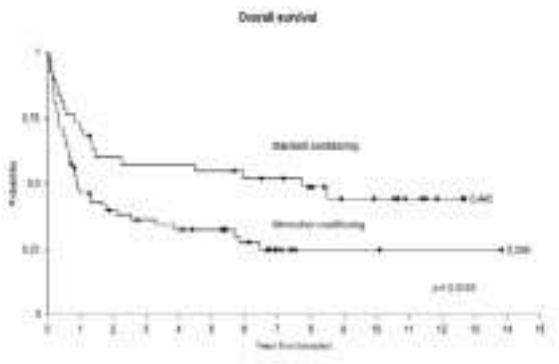

Figure 1. Probability of survival according to standard or alternative conditioning regimens.

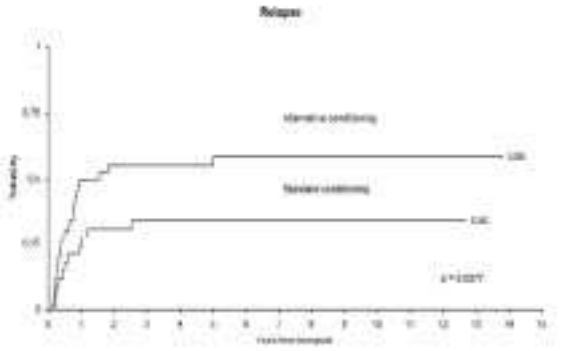

Figure 2. Probability of relapse according to standard or alternative conditioning regimens.

Table 3. Results of univariate analysis.

Endpoint	*Variable*	*p value*
OS	Diagnosis (ALL vs AML)	ns
	Patient sex (male vs female)	ns
	Patient age (< vs > median age)	ns
	Period of SCT (< vs > median date)	ns
	Leukemia phase at SCT (intermediate vs advanced)	0.0133
	Duration of 1st CR (< vs > median time)	0.0294
	Conditioning regimen (standard vs alternative)	0.0163
	GVHD prophylaxis (CsA±PDN vs CsA+MTX±PDN)	ns
	Sex combination (donor female/recipient male vs other)	ns
	Acute GVHD (0 vs 1-2 vs 3-4)	ns
	Chronic GVHD (no vs yes)	0.0157
Relapse	Conditioning regimen (standard vs alternative)	0.0377
TRM	Conditioning regimen (standard vs alternative)	ns

developed a grade 2 acute GVHD. Only 1 patient with AML is alive in CR at 5.8 years from relapse occurring 317 days after SCT and successfully treated with chemotherapy and donor lymphocyte infusion. Sixty-six patients died. The causes of death were: leukemia relapse (n = 38), acute GVHD (n = 9), cerebral hemorrhage (n = 4), chronic GVHD (n = 3), infections (n = 3), multi-organ failure (n = 3), respiratory distress syndrome (n = 3), veno-occlusive disease (n = 1), second tumor (n = 1) and cardiac attack (n = 1). Twenty-six transplant-related deaths occurred at a median of 71 days from SCT (range, 3-2170 days); only 2 of them were observed beyond the 1st year from SCT, at 524 and 2170 days, due to fungal infection and chronic GVHD, respectively. For the 38 survivors, the follow-up ranges from 0.7 to 13.8 years (median of 7.1 years) and the 7-year actuarial probability of OS, relapse and TRM is 36% (95% CI, 26-45%), 48% (95% CI, 37-59%) and 30% (95% CI, 20-40%), respectively.

Univariate analysis

In univariate analysis, the overall survival (OS) was significantly affected by the leukemia phase at time of SCT (p= 0.0133), duration of 1st CR (p = 0.0294), chronic GVHD (p= 0.0157) and conditioning regimen (p = 0.0163) (Table 3). Comparing standard versus alternative regimens, the 7-year probability of OS was 52% vs 25% (95% CI, 36-68% vs 13-37%; p = 0.0163) (Figure 1), that of relapse was 34% vs 58% (95% CI, 18-51% vs 43-73%; p = 0.0377) (Figure 2) and that of TRM was 25% vs 32% (95% CI, 9-40% vs 19-44%; p = ns) (Figure 3). Similar results were obtained in the 87 patients with intermediate phase of acute leukemia at the time of transplantation. For this subgroup of patients the 7-year probability of OS was 58% vs 28% (95% CI, 42-74% vs 14-42%; p = 0.0221), that of relapse was 25% vs 56% (95% CI, 9-41% vs 40-72%; p = 0.017) and of TRM was 25% vs 26% (95% CI, 10-40% vs 14-38%; p = ns).

Multivariate analysis

After adjusting for diagnosis, age, period, leukemia phase, duration of 1st CR, GVHD prophylaxis and donor-recipient sex combination, the use of alternative regimens significantly affected the OS (p = 0.0071) and relapse risk (p = 0.0187) but had no effect on TRM (p = 0.13), even though the risk of TRM was higher in the group prepared with alternative regimens (Table 4).

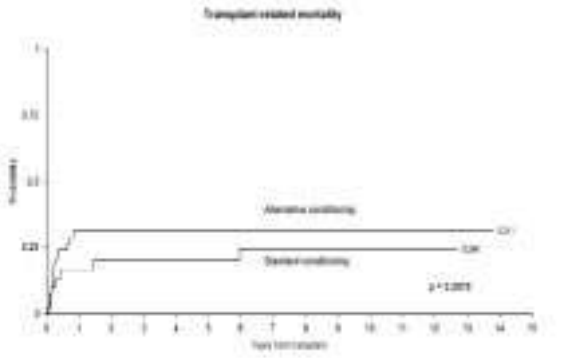

Figure 3. Probability of transplant-related mortality according to standard or alternative conditioning regimens.

Table 4. Overall survival (OS), relapse and transplant-related mortality (TRM) analysis: significance of conditioning regimen adjusting for diagnosis, age, period, leukemia phase, duration of 1st CR, GVHD prophylaxis and donor-recipient sex combination.

	Hazard ratio	*95% confidence interval*	*p*
Death			
Standard regimens	1		
Alternative regimens	2.31	1.26-4.26	0.0071
Relapse			
Standard regimens	1		
Alternative regimens	2.75	1.18-6.38	0.0187
TRM			
Standard regimens	1		
Alternative regimens	2.04	0.8-5.24	0.13

Discussion

In order to reduce the RR after transplantation in patients with acute leukemia prepared with a standard regimen, a number of alternative myeloablative conditionings were adopted in the 1980s and early 1990s. Unfortunately, the patients' outcome did not improve, as any reduction of the RR was usually associated with an increase of the TRM mainly due to the regimen-related toxicity.[21-24] In this study we have retrospectively analyzed the outcome of 104 patients with high-risk acute leukemia who underwent an unmanipulated SCT from an HLA-identical sibling over a 14-year period following a standard or an alternative myeloablative regimen. There are very few studies which examine the outcome of allografting for advanced acute leukemia,[25-32] and only one retrospectively compared the outcome by focusing on different preparative regimens based on two different strategies of GVHD prophylaxis rather than a different conditioning.[29] Our results are consistent with the large retrospective study recently reported by Grigg *et al.*, who analyzed the factors affecting the outcome of allogeneic SCT for adults with refractory and relapsed acute leukemia.[31] In particular in our study the patients with refractory leukemia or very advanced disease at the time of transplant were unlikely to become long-term survivors, with a 5-year probability of < 10%, while the year of transplant did not influence survival. Recurrent leukemia after SCT represented the main cause of failure and was not counteracted by the use of alternative regimens. Indeed, RR and TRM were lower among graft recipients prepared with standard regimens, which in multivariate analysis were found to be significantly associated with better survival. The distribution of patients in the two groups was similar in terms of diagnosis, age, disease phase at time of SCT, duration of 1st CR, GVHD prophylaxis, donor-recipient sex combination and incidence and severity of acute and chronic GVHD. Therefore, the increased likelihood of relapse in recipients of an alternative regimen, confirmed by the adjusted multivariate analysis, might be explained by the significantly lower proportion of these patients, compared to those prepared with a standard regimen, who survived long enough after transplant to be exposed to the risk of chronic GVHD and so harness its immune-therapeutic effect. The lower number of early relapses and regimen-related deaths occurring within 100 days after transplantation in recipients of standard regimens has meant that more patients have been able to take advantage of exposure to chronic GVHD. The importance of GVHD in preventing relapse is widely documented in the literature.[33-35] Particularly, Copelan *et al.* reported that the development of acute and chronic GVHD is an important factor in reducing the post-transplant RR and increasing the long-term leukemia-free survival in patients transplanted in advanced disease.[25] Therefore, it might be strategically useful to aim at decreasing regimen-related toxicity by using reduced intensity conditioning and, consequently, at increasing the proportion of patients who might benefit from the immune-therapeutic GVL effect of chronic GVHD. In this respect, a number of reports have recently been published focusing on the potential benefits of non-myeloablative SCT.[36-40] However, larger cohorts of patients and longer follow-up periods are required to assess the efficacy of the reduced intensity conditioning in advanced acute leukemias, in which the curative potential of such an approach, especially for ALL, is

limited by the spectrum of activity of the GVL reaction, less pronounced in this setting. Therefore, hopefully looking forward to more intensive cell-mediated immune-therapeutic approaches by adoptive transfer of specifically immune rather than naive lymphocytes, the search for more effective but less toxic pre-transplant regimens alternative to the standard ones remains an interesting field of investigation in SCT for advanced acute leukemias.

Contributions and Acknowledgments

AMe and WA contributed equally to this work and should be considered as the principal authors. API was responsible for transplant co-ordination and data collection. CG was responsible for the statistical analyses. AR and RC were responsible for the care of patients. CT, AMi, SF, LL and LDF performed all laboratory investigations. VD was responsible for radiotherapy. All authors contributed in revising the manuscript. They are listed according to a criterion of decreasing individual contribution to the work, with the exception of the last author who had a major role as senior author in interpreting the data. We would like to thank Roberto Ricci and Lorenza Cerilli for their support in producing the figures and carrying out the statistical analyses.

Funding

This work was supported in part by grants from ROMAIL (Associazione Italiana contro le Leucemie-Roma).

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

References

1. Thomas ED, Buckner CD, Banaji M, Clift RA, Fefer A, Flournoy N, et al. One hundred patients with acute leukemia treated with chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood 1977; 49:511-33.
2. Thomas ED, Sanders JE, Flournoy N, Johnson FL, Buckner CD, Clift RA, et al. Marrow transplantation for patients with acute lymphoblastic leukemia in remission. Blood 1979; 54:468-76.
3. Thomas ED, Sanders JE, Flournoy N, Johnson FL, Buckner CD, Clift RA, et al. Marrow transplantation for patients with acute lymphoblastic leukemia: a long-term follow-up. Blood 1983; 62:1139-41.
4. Appelbaum FR, Clift RA, Buckner CD, Stewart P, Storb R, Sullivan KM, et al. Allogeneic marrow transplantation for acute nonlymphoblastic leukemia after first relapse. Blood 1983; 61:949-53.
5. Santos GW, Tutschka PJ, Brookmeyer R, Saral R, Beschorner WE, Bias WB, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med 1983; 309:1347-53.
6. Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. Blood 1987; 70:1382-8.
7. Ringden O, Labopin M, Tura S, Arcese W, Iriondo A, Zittoun R, et al. A comparison of busulphan versus total body irradiation combined with cyclophosphamide as conditioning for autograft or allograft bone marrow transplantation in patients with acute leukaemia. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol 1996; 93:637-45.
8. Vaughan WP, Dennison JD, Reed EC, Klassen L, McGuire TR, Sanger WG, et al. Improved results of allogeneic bone marrow transplantation for advanced hematologic malignancy using busulfan, cyclophosphamide and etoposide as cytoreductive and immunosuppressive therapy. Bone Marrow Transplant 1991; 8:489-95.
9. Hirabayashi N, Goto S, Ishii M, Yuge M, Mitsuma A, Noda N. Busulfan, cyclophosphamide and total body irradiation as conditioning for allogeneic bone marrow transplantation for acute and chronic myeloid leukemia. Bone Marrow Transplant 1998; 21:1079-83.
10. Brown RA, Wolff SN, Fay JW, Pineiro L, Collins RH Jr, Lynch JP, et al. High-dose etoposide, cyclophosphamide and total body irradiation with allogeneic bone marrow transplantation for resistant acute myeloid leukemia: a study by the North American Marrow Transplant Group. Leuk Lymphoma 1996; 22:271-7.
11. Aurer I, Gale RP. Are new conditioning regimens for transplants in acute myelogenous leukemia better? Bone Marrow Transplant 1991; 7:255-61.
12. Blume KG, Kopecky KJ, Henslee-Downey JP, Forman SJ, Stiff PJ, LeMaistre CF, et al. A prospective randomized comparison of total body irradiation-etoposide versus busulfan-cyclophosphamide as preparatory regimens for bone marrow transplantation in patients with leukemia who were not in first remission: a Southwest Oncology Group Study. Blood 1993; 81:2187-93.
13. Horowitz MM, Gale RP, Sondel PM, Goldman JM, Kersey J, Kolb HJ, et al. Graft-versus-leukemia reactions after bone marrow transplantation. Blood 1990; 75:555-62.
14. Kolb HJ, Schattenberg A, Goldman JM, Hertenstein B, Jacobsen N, Arcese W, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. European Group for Blood and Marrow Transplantation Working Party Chronic Leukemia. Blood 1995; 86:2041-50.
15. Mengarelli A, Iori AP, Guglielmi C, Perrone MP, Gozzer M, Girmenia C, et al. Idarubicin intensified BUCY2 regimen in allogeneic unmanipulated transplant for high-risk hematological malignancies. Leukemia 2000; 14:2052-8.
16. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Clift RA, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation 1974; 18:295-304.
17. Shulman HM, Sullivan KM, Weiden PL, McDonald GB, Striker GE, Sale GE, et al. Chronic graft-versus-host syndrome in man. A long-term clinicopathologic study of 20 Seattle patients. Am J Med 1980; 69:204-17.
18. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958; 53:457-81.
19. Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1966; 50:163-70.
20. Cox DR. Regression models and life tables. J R Stat Soc

1972; 34:187-220.
21. Lynch MH, Petersen FB, Appelbaum FR, Bensinger WI, Clift RA, Storb R, et al. Phase II study of busulfan, cyclophosphamide and fractionated total body irradiation as a preparatory regimen for allogeneic bone marrow transplantation in patients with advanced myeloid malignancies. Bone Marrow Transplant 1995; 15:59-64.
22. Demirer T, Buckner CD, Appelbaum FR, Lambert K, Bensinger WI, Clift R, et al. Busulfan, cyclophosphamide and fractionated total body irradiation for allogeneic marrow transplantation in advanced acute and chronic myelogenous leukemia: phase I dose escalation of busulfan based on targeted plasma levels. Bone Marrow Transplant 1996; 17:341-6.
23. Przepiorka D, Ippoliti C, Giralt S, van Beisen K, Mehra R, Deisseroth AB, et al. A phase I-II study of high-dose thiotepa, busulfan and cyclophosphamide as a preparative regimen for allogeneic marrow transplantation. Bone Marrow Transplant 1994; 14:449-53.
24. Carpenter PA, Marshall GM, Giri N, Vowels MR, Russell SJ. Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia conditioned with busulfan, cyclophosphamide and melphalan. Bone Marrow Transplant 1996; 18:489-94.
25. Copelan EA, Penza SL, Elder PJ, Belt PS, Scholl MD, Hehmeyer DM, et al. Influence of graft-versus-host disease on outcome following allogeneic transplantation with radiation-free preparative therapy in patients with advanced leukemia. Bone Marrow Transplant 1996; 18: 907-11.
26. Doney K, Fisher LD, Appelbaum FR, Buckner CD, Storb R, Singer J, et al. Treatment of adult acute lymphoblastic leukemia with allogeneic bone marrow transplantation. Multivariate analysis of factors affecting acute graft-versus-host disease, relapse, and relapse-free survival. Bone Marrow Transplant 1991; 7:453-9.
27. Forman SJ, Schmidt GM, Nademanee AP, Amylon MD, Chao NJ, Fahey JL, et al. Allogeneic bone marrow transplantation as therapy for primary induction failure for patients with acute leukemia. J Clin Oncol 1991; 9:1570-4.
28. Biggs JC, Horowitz MM, Gale RP, Ash RC, Atkinson K, Helbig W, et al. Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. Blood 1992; 80:1090-3.
29. Clift RA, Buckner CD, Appelbaum FR, Schoch G, Petersen FB, Bensinger WI, et al. Allogeneic marrow transplantation during untreated first relapse of acute myeloid leukemia. J Clin Oncol 1992; 10:1723-9.
30. Gale RP, Horowitz MM, Rees JK, Gray RG, Oken MM, Estey EH, et al. Chemotherapy versus transplants for acute myelogenous leukemia in second remission. Leukemia 1996; 10: 13-9.
31. Grigg AP, Szer J, Beresford J, Dodds A, Bradstock K, Durrant S, et al. Factors affecting the outcome of allogeneic bone marrow transplantation for adult patients with refractory or relapsed acute leukaemia. Br J Haematol 1999; 107:409-18.
32. Cornelissen JJ, Carston M, Kollman C, King R, Dekker AW, Lowenberg B, et al. Unrelated marrow transplantation for adult patients with poor-risk acute lymphoblastic leukemia: strong graft-versus-leukemia effect and risk factors determining outcome. Blood 2001; 97:1572-7.
33. Weiden PL, Flournoy N, Thomas ED, Prentice R, Fefer A, Buckner CD, et al. Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow graft. N Engl J Med 1979; 300:1068-73.
34. Atkinson K, Horowitz MM, Gale RP, van Bekkum DW, Gluckman E, Good RA, et al. Risk factors for chronic graft-versus-host disease after HLA-identical sibling bone marrow transplantation. Blood 1990; 75:2459-64.
35. Appelbaum FR. Graft-versus-leukemia (GVL) in the therapy of acute lymphoblastic leukemia (ALL). Leukemia 1997; 11(Suppl 4):15-7.
36. Giralt S, Estey E, Albitar M, van Besien K, Rondon G, Anderlini P, et al. Engraftment of allogeneic hematopoietic progenitors cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 1997; 89:4531-6.
37. Khouri IF, Keating M, Korbling M, Przepiorka D, Anderlini P, O'Brien S, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. J Clin Oncol 1998; 16:2817-24.
38. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. Blood 1998; 91:756-63.
39. McSweeney PA, Wagner JL, Maloney DG, et al. Outpatient PBSC allografts using immunosuppression with low-dose TBI before, and cyclosporine (CSP) and mycophenolate mofetil (MMF) after transplant. Blood 1998; 92 Suppl 1: 519[abstract].
40. Carella AM, Champlin R, Slavin S, McSweeney P, Storb R. Mini-allografts: ongoing trials in humans. Bone Marrow Transplant 2000; 25:345-50.

Peer Review Outcomes

What is already known on this topic

Retrospective studies from international registries and one prospective randomized analysis showed similar outcomes after marrow transplantation using standard vs alternative conditioning regimens, in patients with advanced acute leukemia.

What this study adds

This study confirms previous findings, in a large series from a single institution. Of note, the use of an alternative regimen (etoposide plus total body irradiation, or three-drug combination) was associated with an increased relapse risk after transplant.

Manuscript processing

This manuscript was peer-reviewed by two external referees and by Dr. Jordi Sierra, Deputy Editor. The final decision to accept this paper for publication was taken jointly by Dr. Sierra and the Editors. Manuscript received October 4, 2001; accepted November 6, 2001.

Potential implications for clinical practice

This report supports the use of standard conditioning regimens for patients with high risk acute leukemia submitted to myeloablative hematopoietic transplantation.

Jordi Sierra Gil, Deputy Editor