Allogeneic Bone Marrow Transplantation for Acute Myeloid Leukemia in First Remission: A Randomized Trial of a Busulfan-Cytoxan Versus Cytoxan-Total Body Irradiation as Preparative Regimen: A Report From the Groupe d'Etudes de la Greffe de Moelle Osseuse

By D. Blaise, D. Maraninchi, E. Archimbaud, J. Reiffers, A. Devergie, J.P. Jouet, N. Milpied, M. Attal, M. Michallet, N. Ifrah, M. Kuentz, C. Dauriac, P. Bordigoni, N. Gratecos, F. Guilhot, D. Guyotat, J. Gouvernet, and E. Gluckman for the Group d'Etude de la Greffe de Moelle Osseuse

From October 1987 to December 1990, 101 patients with acute myeloid leukemia (AML) were randomized to be transplanted in first complete remission (CR1). Preparative regimen including Cytoxan (120 mg/kg) with total body irradiation (CYTBI) (N = 50) or busulfan (16 mg/kg) (BUSCY) (N = 51) was followed by allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling. Mean time between diagnosis and BMT was 119 days. The outcome for CYTBI at 2 years is better for probability of disease-free survival (DFS) (72% *v* 47%) ($P < .01$), survival (75% *v* 51%) ($P < .02$), relapse (14% *v* 34%) ($P < .04$), and transplant mortality (8% *v* 27%) ($P < .06$). In multivariable analysis, higher relapse and decreased survival and DFS were associated with BUSCY regimen, while chronic graft-versus-host disease also influenced independently the probability of relapse. This demonstrates the present limitation of busulfan use in this setting, possibly due to probable individual variations in biodisponibility. Furthermore, besides the antileukemic effect of preparative regimens, this trial points out the progress accomplished in BMT management (transplant mortality = 8% in CYTBI) over the last 20 years as well as the effectiveness of transplant in early first CR after CYTBI (DFS = 72% at 2 years).

ALLOGENEIC bone marrow transplantation (BMT) prepared with high-dose cyclophosphamide (CY) followed with total body irradiation (TBI) is a highly efficient therapy for patients suffering from acute myeloid leukemia (AML).[1-5] If BMT is performed during first remission, relapse rate may not go beyond 30%, which is better than any other form of consolidation.[3-6] However, long-term survival is impaired by BMT-related toxicities conducting in most of the series, to a 2- to 3-year disease-free survival (DFS) of only 50% to 55%. Thus, to improve the final outcome of patients receiving transplants for leukemia in first CR, we still need constant efforts to limit transplant mortality. In this direction, several trials, aimed to decrease graft-versus-host disease (GVHD) mortality, pointed out that the benefits of GVHD control were tempered by leukemia recurrence. This shows that progress in the control of transplant complications should be in parallel with developments in the control of leukemia ablation.[7-9]

Toxicities related to usual preparation have been principally imputed to TBI and trials have been conducted to try to replace TBI with chemotherapy. In this field, the association of busulfan (BU) and CY was reported to give a similar or higher leukemic ablation[10-12] than regimens including TBI. Nevertheless, chemotherapy-only and TBI-based regimens have not been prospectively evaluated so far.

For these reasons, the Groupe d'Etude des Greffes de Moelle Osseuse (GEGMO) initiated in 1987 a national prospective trial. This study compares the outcome of patients with AML receiving allogeneic BMT as early consolidation of first complete remission (CR) after a preparation with CY (120 mg/kg) and TBI or BU (16 mg/kg).[11] We report results on 101 consecutive adult patients.

PATIENTS AND METHODS

Patients. To be entered in this trial, patients had to meet the following eligibility criteria: (1) cytologic diagnosis of AML; (2) being in first CR, defined as normal cellular marrow containing less than 5% blasts with normal peripheral blood counts at time of transplant without previous extramedullary relapse; (3) to have an HLA-identical mixed lymphocyte culture (MLC)-negative sibling donor.

Protocol was reviewed by the ethical committee of University of Aix Marseille and consent was obtained from all patients or legal guardians.

Between October 15, 1987 and December 15, 1990, 101 patients above the age of 14 were included in this trial and were randomized before transplant by 15 French centers. Randomization was performed per center. The median age of the population was 32 ± 8 years with a sex ratio (M/F) of 55 to 46. Twenty-eight (29%) had an M4-M5 French-American-British (FAB) subtype. The average of white blood cell (WBC) counts at diagnosis was 28 ± 40 × 10^9/L. Times elapsing between diagnosis and achievement of CR and between diagnosis and BMT were 43 ± 20 and 119 ± 39 days, respectively. Fifteen patients (15%) achieved CR after day 60, ie, after at least a second course of induction. Analysis was conducted after June 15, 1991, giving an average follow-up of 23 ± 11 months with a minimal follow-up of 6 months.

Conditioning regimen. All patients received 60 mg/kg CY intravenously (IV) on each of 2 successive days. For 51 patients (BUSCY group), this was preceded by administration of BU.[11] BU was administered orally at 1 mg/kg/dose over 4 consecutive days for a total dose of 16 mg/kg. For 50 patients (CYTBI group), CY was followed by TBI. Seven patients received a 10 Gy single dose irradiation. Forty-three patients received fractionated TBI to a

From the Bone Marrow Transplantation Unit, Statistical Department and INSERM Unit 119, Institut Paoli Calmettes, Marseille, France.

Submitted November 18, 1991; accepted January 22, 1992.

Supported in part by a grant from the Ligue de Lutte Contre le Cancer.

Address reprint requests to Didier Blaise, MD, Bone Marrow Transplant Unit, INSERM Unit 119, Institut Paoli-Calmettes, 232 Bd Sainte Margueritte, 13273 Marseille Cedex, France.

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "advertisement" *in accordance with 18 U.S.C. section 1734 solely to indicate this fact.*

0006-4971/92/7910-0020$3.00/0

median dose of 12 Gy (range, 11 to 13.5 Gy) in a median of 6 fractions (range, 5 to 6) over a median time of 3 days (range, 3 to 5). Finally, 34 of these patients (79%) received exactly the same TBI regimen (12 Gy in 6 fractions over 3 days). Median dose rate was 5 cGy/min (range, 3 to 25) and all patients had a lung shielding to a median lung dose of 8.8 Gy (range, 6 to 10). Unmanipulated marrow was infused 36 hours after the last day of CY for the BUSCY group or on the last day of TBI.

Posttransplant immunosuppression. All patients received short treatment with methotrexate (MTX) and cyclosporine A (CSA).[9] IV CSA was substituted by the oral drug when tolerated and dose was determined by blood levels. In addition, 17 patients were randomized to receive an anti-P55 monoclonal antibody (MoAb) (33B3.1) from day 1 to day 28.[13,14]

Statistical analysis. Comparisons of means were performed with the *t*-test if the population was normal or with Mann and Whitney u-test. Distribution was compared with χ^2 test and eventually corrected with the Yates method. Kaplan-Meier product-limit estimates were used to estimate the probabilities of engraftment, survival transplant mortality, relapse, and relapse-free survival,[15,16] and differences were tested by the Mantel-Hanzel test.[17] Multivariable analysis was performed using a Cox regression analysis to determine potential factors for risk of relapse, survival, and DFS.[18] Age, sex, FAB subtypes, time between diagnosis and BMT, conditioning regimen, 33B3.1 use, acute GVHD, chronic GVHD, pneumonitis, and venous occlusive disease (VOD) occurrence were used as variables.

RESULTS

Patient characteristics. Table 1 presents characteristics of patients at diagnosis. No statistical difference existed within the two groups for any of these parameters, although some usual parameters were not studied (immunophenotype, cytogenetic, treatment pre-BMT). The majority of the population was composed of early transplants since 63 (62%) patients (CYTBI = 31; BUSCY = 32) were transplanted less than 120 days after diagnosis. No statistical difference was found between this group and the patients transplanted after day 120 in term of patient characteristics and disease presentation. No center effect was seen for patient characteristics or outcome in an analysis taking into account this criteria.

Table 1. Patients, Disease, and Transplant Characteristics

	Study Groups	
	CYTBI (N = 50)	BUSCY (N = 51)
Characteristics at diagnosis (all P = NS)		
Age (yr) (mean ± SD)	32 ± 8	31 ± 8
M/F	32/18	23/28
FAB		
M0-M2	23	30
M3	10	9
M4-M5	16	12
M7	1	0
WBC (×10⁹/L)		
Mean ± SD	34 ± 51	23 ± 32
Patients with WBC > 100	4	3
Duration between diagnosis and BMT (all P = NS)		
Days from diagnosis to CR1 (mean ± SD)	40 ± 18	45 ± 22
Days from diagnosis to BMT (mean ± SD)	120 ± 39	119 ± 38

Abbreviation: NS, not significant.

Table 2. Outcome

	Study Groups	
	CYTBI (N = 50)	BUSCY (N = 51)
Engraftment		
Days to reach 0.5 × 10⁹/L granulocytes	19 ± 6	19 ± 7
Days to reach 50 × 10⁹/L platelets	31 ± 18	30 ± 26
Transplant morbidity and mortality (all P = NS)		
Bacteremia	12	12
Venous occlusive disease	2	6
Interstitial pneumonitis	5	2
Grade ≥2 AGVHD	17	13
Chronic GVHD: N/evaluable	17/45	13/43
Nonleukemic cause of death	5	11
Infection	2	1
Acute GVHD	0	4
Acute GVHD + IP	0	2
Chronic GVHD	0	1
CMV IP	1	0
Venous occlusive disease	1	3
Diabetes mellitus	1	0
Relapse (P < .04)	6	13
KM probability (%)	14	34
Survival (P < .02)	40	30
KM probability (%)	75	51
DFS (P < .01)	39	27
KM probability (%)	72	47

Abbreviations: CMV, cytomegalovirus; IP, interstitial pneumonites.

Transplant characteristics. Donor population had an average age of 32 ± 12 and a sex ratio (M/F) equal to 62 to 39. Forty-five donors were sex mismatched with the recipient. No statistical difference existed within the two groups.

Engraftment. Four patients (CYTBI = 3; BUSCY = 1) died within 1 month and were not analyzable for engraftment, but all had increasing granulocyte counts at time of death. The other 97 patients (97%) had successful sustained engraftment, as documented by the recovery of peripheral granulocyte and platelet counts occurring within the same time range in each group (Table 2).

GVHD. GVHD prophylaxis was identical with the same number of patients receiving anti-p55 MoAb prophylaxis (CYTBI = 8; BUSCY = 9). Overall actuarial probability of grade ≥2 AGVHD was 31% ± 4%, with no difference within the two groups. Eighty-eight patients were valuable for chronic GVHD occurrence after day 100 with a similar incidence among the two groups (Table 2).

Relapse. The probability of relapse censored for other cause of death (Fig 1) is 14% ± 5% in CYTBI group and 34% ± 6% in BUSCY patients (P < .04).

Survival and DFS. Patients dying after relapse were analyzed as dying of leukemia. All other causes of death were related to the transplant. One patient in the CYTBI group was excepted who presented before transplant a very

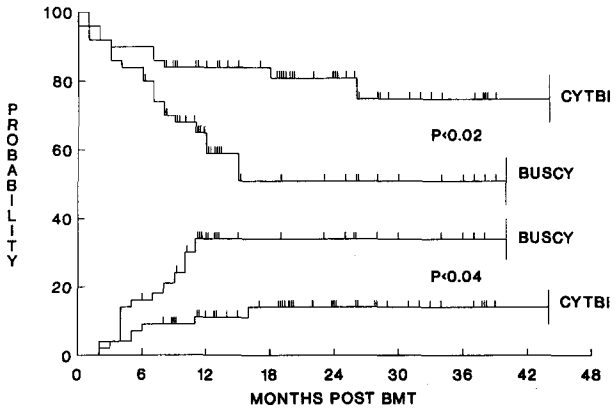

Fig 1. Actuarial probability of relapse (bottom curves) and survival (top curves). Tick marks represent living patients.

unstable diabetes mellitus. He died of this affection more than 2 years after transplant with no evidence of disease recurrence and no evidence of GVHD. The death of this patient is, however, taken into account for survival and DFS probability.

Overall, there is a trend for a higher mortality from nonleukemic cause in the BUSCY group (CYTBI: 8% ± 3%; BUSCY: 27% ± 7%; $P < .06$). Forty-one of the 50 patients in CYTBI group are alive, 40 of them relapse-free, between 8 and 44 months posttransplant. Thirty of the 51 patients in the BUSCY group are alive, 27 of them relapse-free, between 6 and 40 months posttransplant. Kaplan-Meier probability estimates for survival and DFS are presented in Figs 1 and 2 with a significant advantage for patients receiving CYTBI (survival [$P < .02$]: CYTBI, 75% ± 7%; BUSCY, 51% ± 7%; DFS [$P < .01$]: CYTBI, 73% ± 7%; BUSCY, 49% ± 6%).

Effect of time of transplantation on outcome. In this protocol, patients were supposed to receive allogeneic BMT as an early consolidation, as soon as possible after reaching CR1. Actually, the majority of them did so, because 63 (62%) were transplanted before day 120. The overall outcome of patients transplanted before and after day 120 did not differ statistically. However, in patients transplanted within 120 days, differences in outcome between the CYTBI and BUSCY groups were amplified. Transplant mortality was significantly lower in the CYTBI group (CYTBI, 3% ± 3%; BUSCY, 22% ± 7%; $P < .05$) and relapses were increased in the BUSCY group (CYTBI, 14 ± 7; BUSCY, 42 ± 9; $P < .03$). This effect was also seen in both survival (CYTBI, 78% ± 9%; BUSCY, 52% ± 9%; $P < .02$) and DFS (CYTBI, 76% ± 9%; BUSCY, 48% ± 8%; $P < .01$).

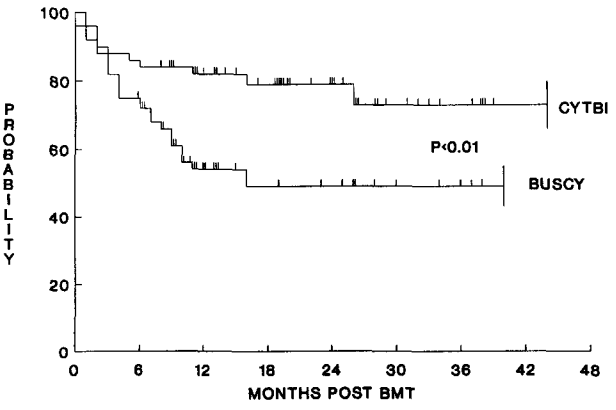

Fig 2. Actuarial probability of DFS. Tick marks represent living patients who did not relapse.

Multivariable analysis. To analyze what covariables may explain the significant differences in the outcome of the two groups a stepwise proportional analysis was performed. Relapse rate is significantly influenced only by two independent factors: chronic GVHD and conditioning regimen (cGVHD better than no cGVHD: $P = .015$; CYTBI better than BUSCY: $P = .049$). Finally, difference in survival and DFS was only related to conditioning regimen (CYTBI better than BUSCY) in a highly significant manner (survival [$P = .012$] and DFS [$P = .009$]).

DISCUSSION

Transplant mortality related to nonrelapse causes remain the principal limitation of allogeneic BMT for early diseases.[19] For this reason the place of allogeneic BMT as therapy of choice in first CR remains under discussion especially for AML and some teams prefer to apply BMT after a failure of conventional therapy.[20,21] However, the antileukemic action of allogeneic BMT is not questionable and is far higher than for chemotherapy.[22] Thus, improvements in BMT-associated toxicity remain an important challenge to improving the outcome of patients suffering from hematologic malignancies.

Practice of BMT over 20 years has permitted substantial benefits in lowering morbidity and mortality both in prophylaxis and management of infections[23-25] and GVHD.[8,9,26] In addition, the search for less toxic conditioning regimens remains worthwhile if they are not associated with higher relapse rate. Furthermore, a regimen without TBI may be of major practical interest to allow transplantation without irradiation facilities.

This trial was designed to compare presently and prospectively a new chemotherapeutical preparation versus a reference conditioning regimen in a multicenter group to bring some answers to these questions. The BUSCY regimen used[11] has been reported to give a high tumor ablation and to be associated with perhaps a lower toxicity than the same BU regimen administered with a high dose of CY.[10] However, concerning toxicity, patients transplanted with the low CY regimen have been treated later and may have benefited of the general and progressive improvements of transplantation.[12] More recently, Copelan et al[27] reported a cohort of 71 patients transplanted for CR1 AML after the same preparation and with a median interval from diagnosis to transplant of 4.5 (range, 1 to 15) months (versus a median of 3.3; range, 2.1 to 7.7 in the present study). GVHD prophylaxis consisted of CSA and prednisone in 61 of the 71 patients.[27] Although probably not statistically different, there is a trend for worse outcome in the present study (DFS = 49% ± 6% *v* 63% ± 12%) and especially for

the probability of relapse (34% ± 6% *v* 14% ± 8%). A shorter interval to perform BMT may explain this last difference, emphasizing that patients surviving in remission for long intervals are less likely to relapse whatever the treatment is.[27] Indeed, comparing in our study the outcome of patients transplanted after BUSCY, the probability of relapse is 43% ± 9% or 18% ± 7% if transplant is performed before or after day 120 (P = NS). The high antileukemic effectiveness of BU has been well demonstrated in murine models. However, the effectiveness of this agent may be probably affected by the wide interpatient variability in plasma levels, especially in children, where higher doses are needed to achieve similar blood levels to adults.[28] Preliminary data suggest that high plasma levels in adults are associated with VOD.[29] Thus, further improvement of BU therapy may be possible but difficult to achieve, without control of individual dosing.

In our study, results in survival and DFS for BUSCY are significantly worse than for CYTBI and are due to a difference in transplant mortality and relapse occurrence. A borderline difference in transplant related deaths exists among the two groups in this report. It may be of interest to see that GVHD represents the principal cause of death reported in the BUSCY group (14%), while incidence of GVHD is similar in the two groups. Unfortunately, very few patients had histologic assessment of death, making it sometimes difficult to discriminate liver GVHD and VOD and to speculate on this point. Finally, transplant mortality in the CYTBI group is under 10%, which is better than data coming from various registries and compiling results of patients transplanted recently as well as more than 5 years ago.[19] In the present study, all patients have been treated since the end of 1987 and could have benefited in both groups from general improvements in supportive care and transplant management. However, in the TBI arm, 86% of the patients received fractionated TBI with lung shielding in 100%. This could contribute greatly to provide in this prospective group better results in terms of transplant mortality than observed in retrospective data from registries. This possible decrease in transplant mortality after TBI was not associated with an increase in relapse rate.

The data in the CYTBI group are, however, different than those observed from the Seattle marrow transplant group. In their study they report an excess in relapse rate of 35% in patients with AML receiving 12 Gy of TBI followed by MTX + CSA.[5] This high relapse rate was not seen when MTX or CSA was used as single agents for prophylaxis of GVHD. The interrelationship between the treatment regimen, GVHD prophylaxis, and relapse is complex, but besides the different activities of preparative regimens, these variations in GVHD prophylaxis may also contribute in part to differences in relapse occurrence. Furthermore, in the present study, patients must not have presented previous extramedullary relapses, which is not specified by Clift et al.[5]

Although follow-up was short, with a mean of 23 months only, this study confirms, if needed, the reproducible results obtained with the classical association of cytoxan and TBI, designed 20 years ago by the Seattle group.[30] It points out, also, progress accomplished in BMT practice during this period and the importance of prospective randomized trials rather than the use of compiled historical controls to evaluate the real impacts of new strategies in BMT.

Finally, besides the comparison of two regimens, this report reinforces the concept that allogeneic BMT used as an early consolidation in AML may lead to high survival rates, disease free,[4,31] and remains the therapy of choice for the subpopulation of patients having HLA-matched siblings.

ACKNOWLEDGMENT

We thank Prof C.D. Buckner and Dr F.B. Petersen for their helpful advice and D. Genre for her help in the data collection. We also thank the BMT units that collaborated on this study from Lyon, Bordeaux, Hôpital St Louis-Paris, Lille, Nantes, Toulouse, Grenoble, Angers, Créteil, Rennes, Nancy, Nice, Poitier, and St Etienne.

REFERENCES

1. Thomas ED, Buckner CD, Clift RA, Fefer A, Johnson FL, Neiman PE, Sale GE, Sanders JE, Singer JW, Shulman H, Storb R, Weiden P: Marrow transplantation for acute nonlymphoblastic leukemia in first remission. N Engl J Med 301:597, 1979

2. Appelbaum FR, Dahlberg S, Thomas ED, Buckner CD, Cheever MA, Clift RA, Crowley J, Deeg HJ, Fefer A, Greenberg PD, Kadin M, Smith W, Stewart P, Sullivan K, Storb R, Weiden P: Bone marrow transplantation or chemotherapy after remission induction for adults with acute non-lymphoblastic leukemia. Ann Intern Med 101:581, 1984

3. Appelbaum FR, Fisher LD, Thomas ED: Chemotherapy versus marrow transplantation for adults with nonlymphocytic leukemia: A five year follow up. Blood 72:174, 1988

4. Reiffers J, Gaspard MH, Maraninchi D, Michallet M, Marit G, Stoppa AM, Corront B, David B, Gastaut JA, Sotto JJ, Brousset A, Carcassonne Y, Holland D: Comparison of allogeneic or autologous bone marrow transplantation and chemotherapy in patients with acute myeloid leukemia in first remission: A prospective controlled trial. Br J Haematol 72:57, 1989

5. Clift RA, Buckner CD, Appelbaum FR, Bearman, SI, Petersen FB, Fisher LD, Anasetti C, Beatty P, Bensinger WI, Doney K, Hill RS, McDonald GB, Martin P, Sanders J, Singer J, Stewart P, Sullivan KM, Witherspoon R, Storb R, Hansen JA, Thomas ED: Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: A randomized trial of two irradiation regimens. Blood 76:1867, 1990

6. Champlin R, Ho W, Gale RP, Winston D, Selch M, Mitsuyasu R, Lenarsky C, Elashoff R, Zighelboim J, Feig SA: Treatment of acute myelogenous leukemia: A prospective controlled trial of bone marrow transplantation versus consolidation chemotherapy. Ann Intern Med 102:285, 1985

7. Martin PJ, Hansen JA, Buckner CD, Sanders JE, Deeg JH, Stewart P, Appelbaum FR, Clift R, Fefer A, Witherspoon RP, Kennedy MS, Sullivan KM, Flournoy N, Storb R, Thomas ED: Effects of in vitro depletion of T cells in HLA identical allogeneic marrow grafts. Blood 66:664, 1985

8. Maraninchi D, Gluckman E, Blaise D, Guyotat D, Rio B, Pico JL, Leblond V, Michallet M, Dreyfus F, Infrah N, Bordigoni A, and GEGMO: Impact of T-cell depletion on outcome of allogeneic BMT for standard risk leukemia. Lancet 2:175, 1987

9. Storb R, Deeg HJ, Whitehead J, Appelbaum F, Beatty P, Bensinger W, Buckner CD, Cliff R, Doney K, Farewell V, Hansen

J, Hill R, Lum L, Martin P, McGuffin R, Sanders J, Stewart P, Sullivan K, Witherspoon R, Yee G, Thomas ED: Methotrexate and cyclosporin compared with cyclosporin alone prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. N Engl J Med 314:729, 1986

10. Santos GW, Tutschka PJ, Brookmeyer R, Saral R, Beschorner WE, Bias WB, Braine HG, Burns WH, Effenbein GJ, Kaizer H, Mellits D, Sensenbrenner LL, Stuart RK, Yeager AM: Marrow transplantation for acute non-lymphoblastic leukemia after treatment with busulfan and cyclophosphamide. N Engl J Med 309:1347, 1983

11. Tutschka PJ, Copelan EA, Klein JP: Bone marrow transplantation following a new busulfan and cyclophosphamide regimen. Blood 70:1382, 1987

12. Santos GW: Marrow transplantation for acute nonlymphoblastic leukemia. Blood 74:901, 1989

13. Blaise D, Maraninchi D, Mawas C, Stoppa AM, Hirn M, Guyotat D, Attal M, Reiffers J: Prevention of acute graft-versus-host disease by monoclonal antibody to interleukine-2 receptor (letter). Lancet 1:1333, 1989

14. Blaise D, Guyotat D, Reiffers J, Olive D, Michallet M, Bellanger C, Vernant JP, Ifrah N, Attal M, Vilmer E, Leblond V, Milpied N, Leporier M, Carosla E, Hirn M, Mawas C, GEGMO: Prospective randomised study of GVHD prevention using an anti-IL2 receptor (CD25) MoAB after allogeneic bone marrow transplantation (BMT). Bone Marrow Transplant 7:150, 1991 (suppl 2)

15. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457, 1958

16. Clift R, Goldman J, Gratwohl A, Horowitz M: Proposals for standardized reporting of bone marrow transplantation for leukemia. Bone Marrow Transplant 4:445, 1989

17. Manzel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163, 1966

18. Cox DR: Regression models and life tables. J R Stat Soc (B) 34:187, 1972

19. Horowitz MM, Bortin MM: Current status of allogeneic bone marrow transplantation, in Terasaki PI (ed): Clinical Transplants 1990. Los Angeles, CA, UCLA Tissue Typing Labatory, 1991

20. Gale RP, Champlin RE: Bone marrow transplantation in acute leukemia. Clin Haematol 15:851, 1986

21. Champlin R, Gale RP: Acute myelogenous leukemia: Recent advances in therapy. Blood 69:1551, 1987

22. Appelbaum FR, Clift RA, Buckner CD, Stewart P, Storb R, Sullivan KM, Thomas ED: Allogeneic bone marrow transplantation for nonlymphoblastic leukemia after first relapse. Blood 61:949, 1983

23. Bowden RA, Sayers M, Flournoy N, Newton B, Banaji M, Thomas ED, Meyers JD: Cytomegalovirus immune globulin and seronegative blood products to prevent cytomegalovirus infection after marrow transplantation. N Engl J Med 314:1006, 1986

24. Meyers JD, Reed ED, Sheep DH, Thornquist M, Dandliker PS,Vicary CA, Flournoy N, Kirk LE, Kersey JH, Thomas ED, Balfour HH: Acyclovir for prevention of cytomegalovirus infection and disease after allogeneic marrow transplantation. N Engl J Med 318:70, 1988

25. Petersen FB, Bowden RA, Thornquist M, Meyers JD, Buckner CD, Counts GW, Nelson N, Newton BA, Sullivan KM, McIver J, Thomas ED: The effect of prophylactic intravenous immune globuline on the incidence of septicemia in marrow recipients. Bone Marrow Transplant 2:141, 1987

26. Blaise D, Olive D, Hirn M, Viens P, Lafage M, Attal M, Stoppa AM, Gabert J, Gastaut JA, Mannoni P, Mawas C, Maraninchi D: Prevention of acute GVHD by in vivo use of anti–interleukin-2 monoclonal antibody (33b3.1): A phase I-II study in 15 patients. Bone Marrow Transplant 8:105, 1991

27. Copelan EA, Biggs JC, Thompson JM, Crilley P, Szer J, Klein JP, Kapoor N, Avalos BR, Cunningham I, Atkinson K, Downs K, Harmon GS, Daly MB, Brodsky I, Bulova SI, Tutschka PJ: Treatment of acute myelocytic leukemia with allogeneic bone marrow transplantation following preparation with BUSCY2. Blood 3:838, 1991

28. Grochow LB, Krivit W, Whitley CB, Blazar B: Busulfan disposition in children. Blood 75:1723, 1990

29. Grochow LB, Jones RJ, Brundrett RB, Braine HG, Chen TL, Saral R, Santos GW, Colvin OM: Pharmacokinetics of busulfan: Correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. Cancer Chemother Pharmacol 25: 55, 1989

30. Thomas ED, Storb R, Clift RA, Fefer A, Johnson FL, Neiman PE, Lermer G, Glucksberg H, Buckner CD: Bone-marrow transplantation. N Engl J Med 292:832, 1975

31. Reiffers J, Maraninchi D, Rigal-Huguet F, Michallet M, Marit G, Stoppa AM, Attal M, Hollard D: Does more intensive treatment cure more patients with acute myeloid leukemia? Semin Hematol 28:90, 1991 (suppl 4)