High Dose Chemotherapy with Busulfan, Cyclophosphamide, and Etoposide as Conditioning Regimen for Allogeneic Bone Marrow Transplantation for Patients with Acute Myeloid Leukemia in First Complete Remission[1]

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Abstract

We explored the combination of busulfan/cyclophosphamide/etoposide as conditioning regimen prior to bone marrow transplantation in 31 patients with acute myeloid leukemia (AML) in first complete remission. The preparative regimen consisted of 16 mg/kg busulfan, 30–60 mg/kg VP-16, and 120 mg/kg cyclophosphamide. With a median follow-up of 30.5 months (range, 5–60 months), 25 patients are alive in continuous complete remission. Estimated disease-free survival at 5 years is 80.5%. Death was due to transplant-related toxicity (graft-*versus*-host disease and cytomegalovirus infection, graft-*versus*-host disease and pneumonia, sepsis and mucositis, respectively). None of the patients have relapsed. As demonstrated by the results of this analysis, the conditioning regimen busulfan/cyclophosphamide/etoposide is effective and well tolerated in patients with AML in first complete remission. Main nonhematological toxicities were mucositis and hepatotoxicity. The low mortality and relapse rate appears to justify allogeneic bone marrow transplantation for patients with AML in first complete remission who have an HLA-identical donor. Whether this regimen offers a substantial improvement in disease-free and overall survival over presently used regimens warrants further investigation.

Introduction

High-dose chemotherapy and total body irradiation, followed by transplantation of hemopoietic stem cells from a histocompatible sibling, has been used in the treatment of acute and chronic leukemias. Long-term disease-free survival has been achieved in 10–20% of patients with relapsed acute leukemia and about 50% of selected patients who received this treatment during first remission of their disease (1–6). High-dose cytoreductive regimens used for allogeneic bone marrow transplantation included the combination of total body irradiation and chemotherapeutic agents like cyclophosphamide, melphalan, piperacinedione, and VP-16[3] as well as high-dose chemotherapy regimens alone without total body radiation, like the combination of cyclophosphamide/BCNU/VP-16 or BuCy (7–17).

The BuCy regimen developed by Santos and Tutschka contains 16 mg/kg bw busulfan and 200 mg/kg bw cyclophosphamide without total body irradiation, which allows for full hemopoietic engraftment, hemopoietic chimerism, and control of leukemia in most patients (11, 12, 13). The modification of this regimen by lowering the cyclophosphamide dose to 120 mg/kg bw appears to be equally effective and less toxic and is the most common conditioning regimen for AMLs (7, 13). The relapse rate of patients with AML transplanted in first remission with this regimen lies between 20 and 30%.

VP-16 has been introduced into high-dose conditioning regimens in combination with busulfan. We explored the combination of busulfan, cyclophosphamide, and VP-16 in patients with AML in first remission (14–18).

The epipodophyllotoxin VP-16 is an ideal drug for use in high-dose therapy because it shows a high antineoplastic activity against a wide range of malignancies and shows a steep dose response and minimal extramedullary toxicity at standard doses (18). Myelosuppression is the main dose-limiting toxicity of VP-16 in standard doses and can be overcome by bone marrow infusion. VP-16 has been administrated in doses up to 60 mg/kg, which constitutes a 10-fold increase over the conventional dos-

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[3] The abbreviations used are: VP-16, etoposide; BuCy, busulfan/cyclophosphamide; BuCyVP, busulfan/cyclophosphamide/VP-16; bw, body weight; AML, acute myeloid leukemia; BMT, bone marrow transplantation; CR, complete remission; GvHD, graft-*versus*-host disease; VOD, venoocclusive disease.

Table 1 Patient characteristics

	Total
Patients	31[a]
Sex	
Male	15
Female	16
Age (yr)	
Median	30
Range	4–51
FAB type	
M1	7
M2	4
M3	—
M4	14
(M4E0)	5
M5	6
M6	5
Not classified	1
Preceeding cycles of chemotherapy	2.6 (1–5)
Dose of VP-16	
30 mg/kg	23
45 mg/kg	6
60 mg/kg	2

[a] Twenty-seven patients received two or three cycles of chemotherapy (TAD, HAM or DAV, MAMAC).

age. The predominant dose-limiting factor of dose escalation is mucositis. Other side effects of this drug in high doses consist of hepatic and pulmonary toxicity, particularly in extensively pretreated patients (18–24).

We explored the combination of busulfan, cyclophosphamide, and VP-16 as a conditioning regimen for bone marrow transplantation in patients with AML in first CR with the aim of reducing the relapse rate without increasing the mortality from the conditioning regimen.

Patients and Methods

Patients. A total of 31 patients (median age, 30 years; range, 4–51 years) underwent allogeneic BMT for AML in first CR between October 1990 and December 1996. Patient characteristics are shown in Table 1. Thirty-one patients received allogeneic bone marrow from a histocompatible sibling. One additional patient received syngeneic bone marrow. The patients included two children: a 4-year-old girl with a Philadelphia chromosome positive AML (FAB M2) and an 11-year-old boy with a secondary leukemia [AML-M5 (primary malignancy, B-non-Hodgkin's lymphoma]. Twenty-seven patients underwent allogeneic BMT for primary AML, and four patients underwent allogeneic BMT for AML following a primary malignancy.

GvHD Prophylaxis. GvHD prophylaxis consisted of cyclosporin A (3 mg/kg) started on day −1, as well as methylprednisone or cyclosporin A (3 mg/kg) started on day −1. Patients received 15 mg/m^2 methotrexate on day 1 and 10 mg/m^2 on days 3, 6, and 11. Acute GvHD was diagnosed and graded according to the Glucksberg criteria (25) and was treated with methylprednisolone and/or anti-thymocyte globuline or with additional anti-tumor necrosis factor in two cases.

Infection Prophylaxis. Infection prophylaxis consisted of ciprofloxacin 2 × 500 mg daily p.o. or ofloxacin 2 × 200 mg daily p.o., fluconazole 2 × 100 mg daily p.o., and amphomoronal suspension p.o. Trimethoprim-sulfamethoxazol 2 × 160 mg daily p.o. was given on three consecutive days. Since 1995 patients additionally received metronidazole, 3 × 400 mg daily, p.o.

Toxicity. Regimen-related toxicity was graded according to the scale of Bearman *et al.* (26).

Conditioning Regimen. The conditioning regimen consisted of 4 mg/kg busulfan on days −8, −7, −6, and −5; 30–60 mg/kg VP-16 on day −4; and 60 mg/kg cyclophosphamide on days −3 and −2. One patient, the boy with the secondary leukemia following a B-non-Hodgkin's lymphoma, suffered from cardiomyopathy and was treated with busulfan and 60 mg/kg VP-16 only. All patients were treated with hematopoietic growth factor granulocyte-colony-stimulating factor, starting on day 1.

The clinical features of the 31 patients treated in first remission are listed in Table 1. Table 2 shows the characteristics of the four patients with secondary AML. Chromosome analysis was done in 20 patients. We found abnormal results in 5 patients: inversion 16 in 2, Philadelphia chromosome in 1, translocation 18:21 in 1, and a deletion (5q26) in 1 patient.

Informed Consent. All patients gave informed consent for this protocol under the guidelines of the Ethikkomittee der Ärztekammer Hamburg.

Preceding Chemotherapy. Patients received induction and consolidation on three German leukemia studies. An average of 2.6 (range, 1–6) chemotherapy cycles were given. Twenty-seven patients received two or three cycles only.

Results

Engraftment. Time to engraftment was defined as the number of days from marrow transplantation until the absolute neutrophil count was sustained above 0.5 × 10^9/L. The median time to absolute neutrophil count greater than 0.5 × 10^9/L was 17 days (range, 9–24). Two patients died before day 28 and were, therefore, not evaluable. The first patient died on day 19 because of grade IV mucositis; the second died on day 25 because of pneumonia. Both patients died in bone marrow aplasia. The median time to reach a platelet count greater than 20,000/μl was 19 days (range, 13–37 days; n = 20) and greater than 50,000/μl, 22 days (range, 16–41 days; n = 20), respectively. Nine patients were discharged before complete platelet recovery (median, day 27; range, days 19–52).

GvHD. Seventeen of the 31 patients receiving allogeneic BMT developed acute GvHD. GvHD >1 occurred in 14 patients (grade II, 10; grade III, 3; grade IV, 1).

Toxicity. Table 3 shows frequency and grade of mucositis and hepatic and renal toxicity. All patients developed severe mucositis requiring continuous morphine infusion. Thirty patients had grade II mucositis. In one patient, mucositis was fatal (grade IV, 30 mg/kg VP-16). Toxic liver dysfunction developed in 24 patients. Grade I hepatic toxicity was seen in 11 patients, and grade II toxicity was seen in 10 patients. Increase of bilirubin was median 4.6 mg/dl (range, 2.2–7.2 mg/dl); the median peak occurred on day 10 (range, days 5–19).

Eight of 24 patients receiving 30 mg/kg VP-16 developed grade I hepatotoxicity; 8 patients developed grade II hepatotox-

Table 2 BMT for secondary leukemia in first CR

First malignancy (ED)	Second leukemia (ED)	Type of BMT	Date of BMT	Age at BMT	aGvHD (Grade)	cGvHD	Complications
B-NHL[a] (11/88)	AML-M5 (6/90)	Allogeneic	1/91	11	+ (II)	+ (general)	
Seminoma	AML-M4eo (8/91)	Allogeneic	4/92	27	+ (II)	+ (general)	Pneumonia (*Aspergillus*)
Embryon, cancer of testis + seminoma	MDS-RAEB-T (1/93)	Allogeneic	6/93	43	+ (II)	+ (general)	
Seminoma (5/91)	AML-M6 (10/93)	Syngeneic	6/94	41	–	–	FUO, GvHD-like lesions

[a] B-NHL, B-non-Hodgkin's lymphoma.

Table 3 Organ toxicity dependent on the dose of VP-16

	All patients (n = 31)	VP-16		
		30 mg/kg (n = 23)	45 mg/kg (n = 6)	60 mg/kg (n = 2)
Mucositis				
Grade I				
Grade II	30	22	6	2
Grade III				
Grade IV	1	1		
Hepatotoxicity				
Grade I	11	8	2	1
Grade II	10	8	2	
Grade III				
VOD	3	1	2	
Max. elevated bilirubin (>2 mg/dl), median (range)	4.6 (2.2–6.8)	5.0 (2.2–7.2)	4.6 (3.2–6.8)	
Renal toxicity				
Grade I	9	8	1	
Grade II	4	4		
Grade III				

icity, including one patient with VOD. Two of six patients receiving 45 mg/kg VP-16 experienced grade I hepatotoxicity. Two patients developed grade II hepatotoxicity; both developed VOD. One of the two patients treated with 60 mg/kg VP-16 developed grade I hepatotoxicity. Renal toxicity grade I developed in 13 patients. An increase in creatinine above twice the baseline value but not requiring dialysis was observed in four patients (grade II).

All patients developed some degree of skin toxicity, ranging from mild reddening of palmar and plantar surfaces and elbows to blister formation on hands and feet. One patient developed toxic pulmonary dysfunction (grade II) with reversible pulmonary infiltrates and severe dyspnea.

Survival. After a median follow-up of 30.5 (5–60) months, 25 of 31 patients are alive in CCR. Six patients died within the first 100 days following treatment-related toxicity (27). Causes of death were GvHD and cytomegalovirus infection, sepsis, mucositis, GvHD, and pneumonia. None of the remaining 25 patients, including the 4 patients transplanted for secondary AML, relapsed. One additional syngeneic BMT for secondary leukemia (Table 2) is alive in CCR 346 days after transplantation. The probability of survival at 5 years is 80.5% (Fig. 1).

Discussion

The combination of BuCyVP followed by BMT is an effective and well-tolerated conditioning regimen for patients with AML in first complete remission. In this analysis of 31 patients with AML in first complete remission, we found that 25 of the 31 patients undergoing an allogeneic BMT are alive in continuous complete remission after a median follow-up of 30.5 months. Six died due to transplant-related toxicity. Not a single relapse occurred.

The efficacy of VP-16 in high dose therapy has been reported in several studies (14–23). VP-16 was initially used as part of preparatory regimens for second allogeneic BMT or high-risk hematological malignancies. In several studies, its high antineoplastic activity in advanced hematological diseases with relatively low relapse rates and superior disease-free survival have been confirmed (17–19). More recently, VP-16 in combination with busulfan has been used to treat adults with acute nonlymphoblastic leukemia with encouraging preliminary results; patients receiving autologous bone marrow (purged with 4-hydroxyperoxycyclophosphamide) had an actuarial disease-free survival of 57% with a relapse rate of 28% (19).

The results of our analysis show a 0% relapse rate and low mortality in patients transplanted for AML in first complete remission. In interpreting these results, several factors must be considered, *i.e.*, the limited number of patients and the design as an uncontrolled study. Furthermore, patients with AML in first complete remission independent of prognostic factors were included, which may cause a selection bias (5, 28–30). For example, because of the retrospective design of this investigation, chromosomal analyses were available in only 20 of 31

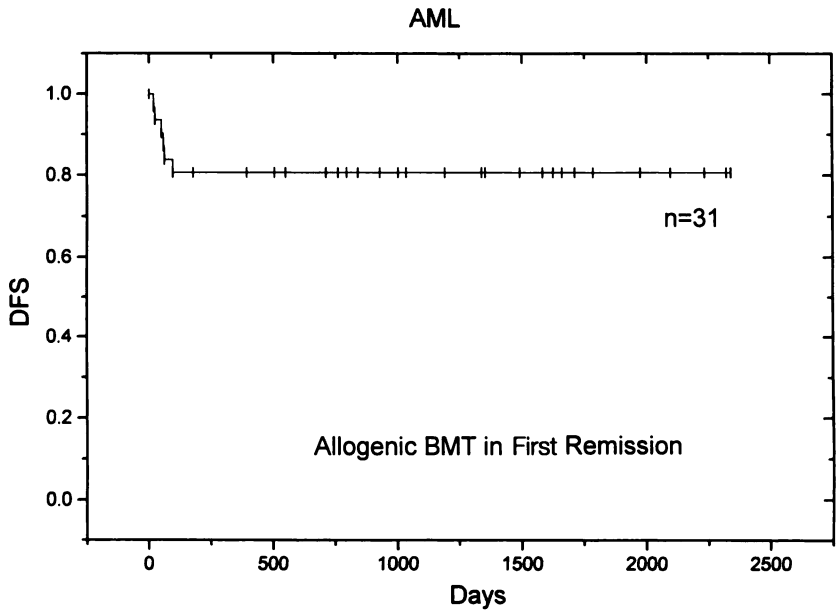

Fig. 1 Disease-free survival of patients transplanted in first remission (n = 31).

patients. Therefore, we cannot exclude that our results may depend on an accidental selection of patients with a good prognosis. Nevertheless, as described above, the conditioning regimen consisting of BuCyVP appeared as an effective treatment (21), and our results may be due to the introduction of VP-16 into the standard conditioning regimen. As published recently, allogeneic BMT for AML in first complete remission can significantly improve disease-free survival, but as a result of the high treatment-related mortality, overall survival is comparable to the results of autologous BMT and conventional therapy (4, 16). In our analysis, fatal treatment-related toxicity after allogeneic BMT was 20%. Consistent with the results of other investigators (21, 23), major nonhematological toxicities following high-dose VP-16 were severe mucositis and hepatic dysfunction. Skin toxicity was seen frequently but was commonly mild.

In several studies, a dose-dependent increase in extramedullary toxicity was described, with a maximum tolerated dose of 60–70 mg/kg VP-16 (14–16, 20–25). We found no marked difference with regard to different doses of VP-16, ranging from 30–60 mg/kg. In our study, a grade II mucositis developed in 30 of 31 patients. Mucositis was fatal in one patient treated with the lowest dose of VP-16 (30 mg/kg). There was no significant increase of incidence and grade of hepatotoxicity related to different doses of VP-16. Because of the small number of patients, the influence of the dose of VP-16 (30 *versus* 45 *versus* 60 mg/kg) on hepatic toxicity cannot be determined statistically.

Moreover, there are several other factors that can cause liver dysfunction in the course of BMT, *i.e.,* busulfan, GvHD, infection, or prior liver injury (1, 2, 31–33). Whether there is an increase in hepatic toxicity caused by dose escalation of VP-16 requires further investigation. Recently, the report of an increase in severe pulmonary toxicity with pulmonary hemorrhage following high-dose VP-16 in patients, especially with a history of prior chest irradiation or abnormal lung function, has been published (23). In our analysis, we observed one life-threatening case of toxic pulmonary dysfunction (grade II) in a patient who had severe pneumonia and atelectasis prior to BMT, but we could not prove whether this event was due to the toxicity of VP-16. Nevertheless, the regimen-related toxicity that was observed in this investigation was comparable to the results of studies using BuCy alone (7, 11–13).

We analyzed a conditioning regimen consisting of BuCyVP, followed by BMT, as treatment for AML in first complete remission. The low mortality and low relapse rate observed demonstrate that postremission treatment with BuCyVP-16 and BMT is a well-tolerated and highly effective regimen but is also associated with skin and liver toxicity. Whether this regimen offers a substantial improvement in disease-free and overall survival compared to presently used regimens warrants further investigation.

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References

1. Büchner, T., Urbanitz, D., Hiddemann, W., *et al.* Intensified induction and consolidation with or without maintenance chemotherapy for acute myeloid leukemia (AML): two multicenter studies of German AML Cooperative Group. J. Clin. Oncol., *3:* 1583–1589, 1985.

2. Cassileth, P. A., Lynch, E., Hines, J. D., Oken, M. M., Mazza, J. J., Bennett, J. M., McGlave, P. B., Edelstein, M., Harrington, D. P., and O'Connell, M. J. Varying intensity of postremission therapy in acute myeloid leukemia. Blood, *79:* 1924–1930, 1992.

3. Champlin, R. E., Gajewski, J., Nimer, S., Vollset, S., Landaw, E., Winston, D., Schiller, G., and Ho., W. Postremission chemotherapy for adults with acute myelogenous leukemia: improved survival with high-dose cytarabine and daunorubicin consolidation treatment. J. Clin. Oncol., *8:* 1199–1206, 1990.

4. Mayer, R. J., Davis, R. B., Schiffer, C. A., Berg, D. T., Powell, B. L., Schulman, P., Omura, G. A., Moore, J. O., McIntyre, O. R., and Frei, E. Intensive postremission chemotherapy in adult with acute myeloid leukemia. N. Engl. J. Med., *331:* 896–903, 1994.

5. McGlave, P. B., Haake, R. J., Bostrom, B. C., Kersey, J. H., *et al.* Allogeneic bone marrow transplantation for acute nonlymphocytic leukemia in first remission. Blood, *72:* 1512–1517, 1988.

6. Clift, R. A., Buckner, C. D., Appelbaum, F. R., Bearman, S. I., Petersen, F. B., Fisher, L. D., Anasetti, C., Beatty, P., Bensinger, W. I., Doney, K., *et al.* Allogeneic bone marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. Blood, *76:* 1876–1871, 1990.

7. Copelan, E. A., Biggs, J. C., Thompson, J. M., Crilley, P., Szer, J., Klein, J. P., Kapoor, N., Avalos, B. R., Cunningham, I., Atkinson, K., *et al.* Treatment for acute myeloid leukemia with allogeneic bone marrow transplantation following preparation with BuCy2. Blood, *78:* 838–843, 1991.

8. Appelbaum, F. R., Fisher, L. D., Thomas, E. D., and Seattle Marrow Transplant Team. Chemotherapy *versus* marrow transplantation for adults with acute nonlymphocytic leukemia: a five year follow-up. Blood, *72:* 179, 1988.

9. Zander, A. R., Keating, M., Dicke, K., Freireich, E. J., *et al.* A comparison of marrow transplantation with chemotherapy for adults with acute leukemia of poor prognosis in first complete remission. J. Clin. Oncol., *6:* 1548–1557, 1988.

10. Zittoun, R. A., Mandelli, F., Willemze, R., de Witte, T., Labar, B., Resegotti, L., Leoni, F., Damasio, E., Visani, G., Papa, G., Sugio, S., *et al.* Autologous or allogeneic bone marrow transplantation compared with intensive chemotherapy in acute myelogenous leukemia. N Engl J Med, *332:* 217–223, 1995.

11. Santos, G. W. The development of busulfan/cyclophosphamide preparative regimens. Semin. Oncol., *4* (Suppl. 4)*:* 12–16, 1993.

12. Santos, G. W., Tutschka, P. J., Brookmeyer, *et al.* Marrow transplantation for acute non-lymphomic leukemia after treatment with busulfan and cyclophosphamide. N. Engl. J. Med., *309:* 1347–1353, 1983.

13. Tutschka, P. J., Copelan, E. A., Klein, J. A., *et al.* Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimen. Blood, *70:* 1382–1388, 1987.

14. Blume, K. G., and Forman, S. J. High-dose busulfan, etoposide as a preparative regimen for second bone marrow transplantation in hematologic malignancies. Blood, *55:* 49–53, 1987.

15. Blume, K. G., Forman, S. J., O'Donnel, M. R., Doroshow, J. H., *et al.* Total body irradiation and high-dose etoposide: a new preparative regimen for bone marrow transplantation in patients with advanced hematological malignancies. Blood, *69:* 1015–1020, 1987.

16. Chao, N. J., Stein, A. S., Long, G. D., Negrin, R. S., Amylon, M. D., Wong, R. M., Forman, S. J., and Blume, K. G. Busulfan/etoposide–initial experience with a new preparatory regimen for autologous bone marrow transplantation in patients with AnLL. Blood, *81:* 319–323, 1993.

17. Linker, C. A., Ries, C. A., Damon, L. E., Rugo, H. S., and Wolf, J. L. Autologous bone marrow transplantation for acute myeloid leukemia using busulfan plus etoposide as a preparative regimen. Blood, *81:* 311–318, 1993.

18. Stadtmauer, E. A., Casselith, P. A., and Gale, R. P. Etoposide in leukemia, lymphoma and bone marrow transplantation. Leuk. Res., *13:* 639–650, 1989.

19. Henwood, J. N., and Brodgen, R. N. Etoposide: a review of ist pharmacodynamic and pharmacokinetic properties, and therapeutic potential in combination chemotherapy of cancer. Drugs, *39:* 438–490, 1990.

20. Wolff, S. N., McKay, C. M., Hande, K. R., *et al.* High-dose VP-16–213 and autologous bone marrow transplantation for refractory malignancies–a phase I study. J. Clin. Oncol., *1:* 701–705, 1983.

21. Spitzer, T. R., Cottler-Fox, M., Torrisi, J., *et al.* Escalating doses of etoposide with cyclophosphamide and fractionated TBI or busulfan conditioning for BMT. Bone Marrow Transplant., *4:* 559–565, 1989.

22. Brown, R. A., Herzig, R. H., Wolff, S. N., Frei-Lahr, D., Pineiro, L., Bolwell, B. J., Lowder, J. N., Harden, E. A., Hande, K. R., and Herzig, G. P. High-dose etoposide and cyclophosphamide without bone marrow transplantation for resistant hematologic malignancy. Blood, *76:* 473–479, 1990.

23. Crilley, P., Topolsky, D., Styler, M. J., Bernstein, E., Resnick, K., Mullaney, R., Bulova, S., Brodsky, I., and Marks, D. I. Extramedullary toxicity of a conditioning regimen containing busulphan, cyclophosphamide and etoposide in 84 patients undergoing autologous and allogeneic bone marrow transplantation. Bone Marrow Transplant., *15:* 361–365, 1995.

24. Imrie, K. R., Couture, F., Turner, C. C., Sutcliffe, S. B., and Keating, A. Peripheral neuropathy following high-dose etoposide and autologous bone marrow transplantation. Bone Marrow Transplant., *13:* 77–79, 1995.

25. Glucksberg, H., Storb, R., Fefer, A., *et al.* Clinical manifestations of graft *vs.* host disease in human recipients of marrow from HLA-matched sibling donors. Transplantation, *18:* 295, 1974.

26. Bearman, S. I., Appelbaum, F. R., Buckner, C. D., *et al.* Regimen-related toxicity in patients undergoing bone marrow transplantation. J. Clin. Oncol., *6:* 1562–1568, 1988.

27. Kaplan, E., and Meyer, P. Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc., *53:* 457–481, 1985.

28. Keating, M. J., Smith, T. L., Kantarjian, H., *et al.* Cytogenetic pattern in acute myelogenous leukemia: a major reproducible determinant of outcome. Leukemia (Baltimore), *2:* 403–412, 1988.

29. Clift, R. A., Buckner, C. D., Thomas, E. D., *et al.* The treatment of acute non-lymphoblastic leukemia by allogeneic bone marrow transplantation. Bone Marrow Transplant., *2:* 243, 1987.

30. Bloomfield, C. D., Lawrence, D., Arthur, D. C., Berg, D. T., Schiffer, C. A., and Mayer, R. J. Curative impact of intensification with high-dose cytarabine in acute myeloid leukemia (AML) varies by cytogenetic group. Blood, *84* (Suppl. 1): 111a, 1994.

31. Grochow, L. B., Jones, R. J., Brundett, *et al.* Pharmacokinetics of busulfan: correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. Cancer Chemother. Pharmacol., *25:* 55–61, 1989.

32. McDonald, G. B., Hinds, M. S., Fisher, L. D., Schoch, H. G., Wolford, J. L., Banaji, M., Hardin, B. J., Shulman, H. M., and Clift, R. A. Veno-occlusive disease of the liver and multiorgan failure after bone marrow transplantation: a cohort study of 355 patients. Ann. Intern. Med., *118:* 255–267, 1993.

33. Baglin, T. P. Veno-occlusive disease of the liver complicating bone marrow transplantation. Bone Marrow Transplant., *13:* 1, 1994.

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