Bone Marrow Transplantation, (1997) 20, 107–112

Risk of extramedullary relapse following allogeneic bone marrow transplantation for acute myelogenous leukemia with leukemia cutis

G Michel[1], F Boulad[1], TN Small[1], P Black[1], G Heller[1], H Castro-Malaspina[2], BH Childs[2], AP Gillio[1], EB Papadopoulos[2], JW Young[2], NA Kernan[1] and RJ O'Reilly[1]

Memorial Sloan-Kettering Cancer Center, Departments of [1]Pediatrics and [2]Medicine, Bone Marrow Transplantation Service, New York, USA

Summary:

Leukemia cutis (LC) is a rare feature of acute myeloblastic leukemia (AML). Little information is available regarding its prognostic influence on post-transplant outcome. In our institution, 202 patients with AML received an allogeneic HLA-identical marrow transplant from related donors between March 1982 and January 1994. Thirteen patients had prior leukemic involvement of the skin (leukemia cutis or LC group) while 189 patients did not (non-LC group). There was a higher incidence of patients with the M4-M5 FAB subtypes in the LC group (83%) as compared to the non-LC group (33%). In addition, the percentage of patients transplanted in relapse was also higher in the LC group (69 *vs* 15%). While there were no differences observed in the rates of relapse post-transplant in the LC and non-LC groups when matched for stage of disease at transplant, the sites of relapse differed markedly. Five of six relapses in the LC group involved extramedullary sites as compared to only six of 38 relapses in the non-LC group ($P = 0.002$), with a 6-year probability of extramedullary relapse of 38.5% in the LC group as compared to 3.9% in the non-LC group. This increased probability of extramedullary relapse was independent of the FAB morphology (50 *vs* 2% for patients with the M4-M5 subtypes in the LC and the non-LC group respectively) and of disease status at the time of transplant. Moreover, only three relapses post-transplant involved the skin, all of which were in the LC group, with a probability of skin relapse of 23.1% in this group. Patients with AML and leukemia cutis have a remarkable propensity to relapse in extramedullary sites following marrow transplantation. These relapses occur in the skin as well as other organs. Further investigations are needed to understand the biological basis of this clinical feature.

Keywords: acute myelogenous leukemia; bone marrow transplant; leukemia cutis

Leukemia cutis (LC) is a rare feature of acute myeloblastic leukemia (AML),[1–8] with an incidence estimated to be 2–11%.[9–11] It occurs more frequently in patients with the M5 FAB subtype and in infants with AML, the incidences being 31 and 46%, respectively.[12–13]

Few studies have evaluated the outcome of patients with LC. The largest published series describes 18 patients with AML and LC who were treated with conventional therapy and who experienced a high incidence of serial skin relapses, suggesting that skin could provide a sanctuary site for leukemic cells.[14] While patients with acute myeloblastic or lymphoblastic leukemia with prior involvement of extramedullary sites such as CNS or testis treated with BMT have been reported to have an increased risk of extramedullary relapse post-transplantation,[15,16] the outcome of patients with a history of LC treated with marrow transplantation has not been described previously.

We report a single institution retrospective analysis of 13 patients with AML and LC who underwent allogeneic BMT at Memorial Sloan-Kettering Cancer Center (MSKCC). The overall relapse rates and sites of relapse that occurred in this group were compared with those observed in 189 consecutive patients with AML without LC who were treated with allogeneic BMT during the same time period.

Patients and methods

Patient groups were drawn from a series of 202 consecutive adults and children who received HLA-matched related bone marrow transplants for the treatment of AML between March 1982 and January 1994. Of these, 13 had a history of leukemia cutis (LC). The other 189 patients without such a history constituted the non-LC control group.

Patient characteristics

Characteristics of the patients in the LC and non-LC groups are compared in Table 1. Of the 13 patients in the LC group, eight were female and five were male. Mean WBC count at diagnosis was $38.7 \pm 13.8 \times 10^9$/l (range 0.9 to 139×10^9/l). The distribution of FAB subtypes in 12 evaluable patients was as follows: two with M2, three with M4, and seven with M5. One patient had CNS involvement at diagnosis. As shown in Table 2, LC was present at the time of diagnosis in all but one patient (UPN1493) who developed LC at the time of relapse. Five of the 12 patients who had LC at the time of diagnosis experienced at least

Correspondence: Dr F Boulad, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021, USA
Received 27 November 1996; accepted 12 March 1997

Table 1 Patient and treatment characteristics: comparison of the two patient groups

	Non-LC group (n = 189)	*LC group (n = 13)*	*Statistics (P value)*
WBC at diagnosis			
Evaluable (*n*)	179	12	
Mean ± s.e.m.	31.2 ± 3.6	38.7 ± 13.8	NS[a]
FAB subtypes			
Evaluable (*n*)	148	12	
M4-M5/other subtypes (*n*)	49/99	10/2	<0.001[b]
% M4-M5	33%	83%	
Age at BMT			
Mean ± s.e.m.	26.7 ± 1	26.1 ± 4	NS[a]
<20 years (%)	30%	31%	NS[b]
Status at BMT			
CR/Relapse (*n*)	160/29	4/9	
% CR	85%	31%	<0.001[b]
Cytoreduction			
TBI/no TBI	175/14	11/2	NS[b]
% TBI	93%	85%	
T cell depletion			
Yes/No	122/67	6/7	
% T cell depleted	65%	46%	NS[b]

LC = leukemia cutis; WBC = white blood cell count; CR = complete remission; TBI = total body irradiation; s.e.m. = standard error of mean.
[a]According to the Wilcoxon rank sum test.
[b]According to the Fisher's exact test.

one leukemic recurrence in the skin before transplant. Four patients were transplanted in first ($n = 2$) or second ($n = 2$) complete remission (CR), and nine were transplanted in relapse. Among the nine patients transplanted in relapse, four were in bone marrow relapse with no skin involvement, three were in marrow remission but with skin disease, and two patients had both marrow and skin involvement at the time of BMT. The mean age at the time of BMT for the LC group was 26.1 ± 4 years (range 1–44 years).

For the 189 patients in the non-LC group, the mean WBC count at diagnosis was 31.2 ± 7, not significantly different from that of the LC group. The proportion of patients with the M4–M5 FAB subtypes, however, was lower (33 *vs* 83%, $P < 0.001$). The proportion of patients transplanted in CR was also higher than that of patients in the LC group (85 *vs* 31%, $P < 0.001$). The mean age at BMT was comparable to that of the LC group.

Treatment characteristics

Patients in the LC and non-LC groups received transplants according to protocols evaluating different treatment strategies for AML at specific stages of its progression. In brief, 186 patients including 11 in the LC group and 175 in the non-LC group received a hyperfractionated total body irradiation (HFTBI) containing regimen as previously described.[17,18] Patients transplanted before 1985 received 11 fractions to a total dose of 1375 cGy, and the rest received 12 fractions to a total of 1500 cGy. All patients had lung shielding to reduce the dose to the lungs to 800–900 cGy. Overlying ribs were treated with a 600 cGy boost using high energy electrons to increase the total dose to the chest wall to approximately 1500 cGy. Male patients also received a 400 cGy testicular boost with electrons.

In the LC group, 11 of 13 patients received HFTBI and two of these 11 patients with active skin disease received an additional 400 cGy whole skin electron boost. Following HFTBI, patients were treated with cyclophosphamide (60 mg/kg/day × 2) alone in six cases, thiotepa (5 mg/kg/day × 2) and cyclophosphamide in three cases as previously described,[19] thiotepa and etoposide or aziridinylbenzoquinone (AZQ) and cyclophosphamide in two cases. The two patients who did not receive TBI were conditioned with busulfan and cyclophosphamide in association with high-dose cytarabine in one patient and with a radio-iodinated anti-CD33 monoclonal antibody (^{131}I-M195) in the other, as previously described.[20] Six patients received a T cell-depleted marrow graft for the prevention of graft-versus-host disease (GVHD) as previously described.[21,22] For the seven remaining patients, GVHD prophylaxis consisted of different combinations of cyclosporin A, methotrexate and steroids as specified in the protocols used at our institution at the time of their transplants. Acute and chronic GVHD were evaluated according to standard published criteria,[23,24] and treated with immunosuppressive therapy when indicated.

For the non-LC group, 175 patients (93%) received HFTBI-containing regimens with the addition of cyclophosphamide alone ($n = 103$), thiotepa and cyclophosphamide ($n = 33$), etoposide and cyclophosphamide ($n = 22$), AZQ and cyclophosphamide ($n = 14$), and cytarabine and cyclophosphamide ($n = 2$). Seven patients received busulfan and cyclophosphamide and seven patients were treated with busulfan, cyclophosphamide and ^{131}I-anti-CD33. GVHD prophylaxis consisted of T cell-depleted marrow transplants in 122 patients (65%); the remaining patients received unmodified grafts and pharmacologic GVHD prophylaxis with the addition of cyclosporine and/or methotrexate

and/or steroids. These numbers were not significantly different from the LC group.

Statistical methods

The probability of disease-free survival (DFS) was calculated using the method of Kaplan–Meier.[25] The probabilities of relapse, extramedullary relapse and skin relapse were estimated with the method of competing risks.[26] Distributions of qualitative variables between two groups were compared according to the Fisher's exact test; comparisons of continuous variables were made using the Wilcoxon rank sum test.[27] Extramedullary relapse and skin relapse were defined as extramedullary or skin leukemia occurring as the first site of disease recurrence or recurring simultaneously with disease in the marrow. Non-chloromatous liver, spleen or lymph node involvement occurring concomitantly with a marrow relapse were not taken into consideration for the purpose of our analysis, and these patients were classified as relapsing in the marrow. Similarly, patients who relapsed initially in the bone marrow and then went on to develop extramedullary disease were also classified as relapsing in the marrow.

Results

The outcome of the marrow transplants administered to the 13 patients with LC is detailed in Table 2. The Kaplan–Meier estimate of disease-free survival (DFS) at 5 years for this group was $23.1 \pm 21\%$, with an overall relapse rate of $46.2 \pm 28\%$ at 5 years.

As can be seen, of four patients transplanted in remission in the LC group, one died of BMT-related toxicity (veno-occlusive disease), one relapsed in the skin and marrow 7 months post-transplant, and two patients survive disease-free 15 and 20 months post-transplant. In comparison, of 160 patients in the non-LC group transplanted in primary to tertiary remission, 78 survive disease-free. The probability of 5-year disease-free survival (DFS) for this larger group was $46 \pm 8\%$ and the probability of relapse at 5 years was $17 \pm 6\%$. The risk of extra-medullary relapse in the non-LC patients transplanted in remission was $4.5 \pm 3.6\%$ with no relapses involving the skin.

Of the nine patients in the LC group transplanted in relapse, only one survives disease-free 127 months post-transplant. In this group, three patients succumbed to transplant-related toxicity, including interstitial pneumonia ($n = 2$) and pulmonary hemorrhage ($n = 1$). Five patients experienced disease recurrence 2–5 months post-transplant. The 5-year estimated probability of relapse in this group was $56 \pm 33\%$. Four of the five relapses occurred in extramedullary sites including the skin alone ($n = 1$), skin and marrow ($n = 1$), a solid tumor involving the soft tissue of the face and the left petrous bone ($n = 1$) and a chloroma of the breast ($n = 1$). However, sites of skin relapse were different from sites identified prior to transplant. By comparison, of 29 patients in the non-LC group transplanted in relapse, 13 patients recurred post-transplant with a risk of relapse of $48 \pm 20\%$ at 5 years, and a DFS of $16 \pm 14\%$. There were no extramedullary relapses recorded in this group.

While there were no differences observed in the rates of relapse post-transplant in the LC and non-LC groups when matched for stage of disease at transplant (Table 3 and Figure 1a), five of the six relapses in the LC group involved an extramedullary site, as compared to only six of 38 relapses observed in the non-LC group ($P = 0.002$). The probability of extramedullary relapse was $38.5 \pm 27\%$ for the LC group and $3.9 \pm 3.2\%$ for the non-LC group. All three relapses which involved the skin post-transplant occurred in the LC group with a probability of skin relapse post-transplant of $23.1 \pm 23\%$ in the LC group and 0% for the non-LC patients (Figure 1b).

Because the proportion of patients with the M4-M5 FAB

Table 2 Characteristics and outcome of 13 patients with leukemia cutis

UPN	*Age BMT (years)*	*FAB subtype*	*Time of onset of LC Dx/Rel*	*Status at BMT*			*Skin RT*		*Outcome post-BMT (months)*
				Overall	*Skin*	*BM*	*Before BMT*	*At BMT*	
BMT in remission (CR)									
1253	44	M5	Dx	CR1	No	No	No	No	Alive and well (20+)
1352	28	M2	Dx	CR1	No	No	No	No	Alive and well (15+)
735	35	M5	Dx	CR2	No	No	Yes (L)	No	Relapse skin + BM (7)
842	35	M2	Dx/Rel	CR2	No	No	Yes (L)	No	Toxic death (1)
BMT in relapse (Rel)									
382	15	M4	Dx	Rel1	No	Yes	Yes (L)	No	Alive and well (127+)
918	1.6	M5	Dx	Rel3	No	Yes	No	No	Relapse chloroma (4)
1096	42	M4	Dx	Refract	No	Yes	No	No	Toxic death (1)
1336	34	?	Dx	Refract	No	Yes	No	No	Relapse BM (5)
254	33	M5	Dx/Rel	Rel1	Yes	No	No	TSEB	Toxic death (1)
450	21	M5	Dx/Rel	Rel1	Yes	No	No	No	Relapse skin (2)
320	14	M5	Dx/Rel	Rel2	Yes	No	TSEB	TSEB	Relapse chloroma (2)
1263	36	M5	Dx/Rel	Rel2	Yes	Yes	Yes (L)	No	Toxic death (9)
1493	1	M4	Rel	Rel2	Yes	Yes	No	No	Relapse skin + BM (2)

RT = radiation therapy; DX = diagnosis; Rel = relapse; CR = complete remission; (L) = localized radiation; TSEB = total skin electron beam therapy.

Table 3 Extramedullary relapses

	Patient No.	*Probability of extramedullary relapse*[a]	*No. extramedullary relapses/ total No. of relapses*
LC patients			
Overall	13	38.5 ± 27 %	5/6
Non-LC patients			
Overall	189	3.9 ± 7.8%	6/38
BMT in CR	160	4.5 ± 3.6%	6/25
BMT in relapse	29	0%	0/13
M4-M5 subtypes			
All patients (LC + non-LC)	59	10.2 ± 7.8%	6/16
LC patients	10	50 ± 31.6%	5/5
Non-LC patients	49	2 ± 2.0%	1/11
Other FAB subtypes	101	4.3 ± 4.0%	3/22

[a]Probabilities of extramedullary relapse are calculated with the method of competing risks.

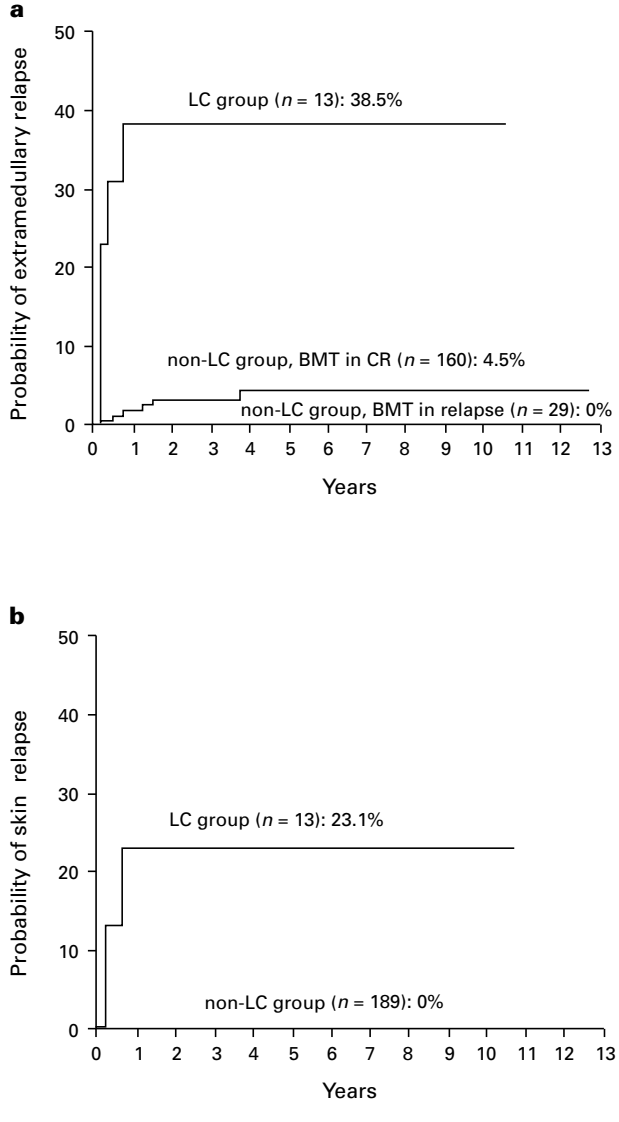

Figure 1 Probability of relapse post-transplant. (**a**) Probability of extramedullary relapse in patients without leukemia cutis transplanted in remission or in relapse and in patients with leukemia cutis. (**b**) Probability of skin relapse in patients with or without leukemia cutis.

subtypes was higher in the LC group, we also evaluated the probability of extramedullary relapse with respect to FAB subtypes. When all patients from the LC and non-LC groups were considered, the probability of extramedullary relapse was 10.2 ± 7.8% for patients with the M4-M5 FAB subtypes and 4.3 ± 4% for patients with the other subtypes. However, the risk of extramedullary relapse for patients in the LC group with the M4-M5 subtypes was 50 ± 32%, as compared to 2 ± 2% for the non-LC patients with the M4-M5 subtypes.

Discussion

The purpose of this study was to analyze the relapse risk of 13 patients with AML and LC who underwent an allogeneic marrow transplant at our institution and compare it with that of 189 consecutive patients with AML but without a history of LC treated similarly at our institution during the same time period.

In this series, the percentage of patients transplanted in remission in the non-LC group was higher than in the LC group. When patients were matched for stage of disease at transplant, a previous history of LC did not influence the overall relapse rate or disease-free survival after BMT, but was associated with a remarkable propensity for relapses in extramedullary sites. This observation suggests that patients with LC do not have disease that is more aggressive than that of other patients with AML, but that the clinical expression of their disease after BMT is different.

In one series of 18 patients with AML and LC treated with chemotherapy alone or with chemotherapy and skin irradiation,[14] eight patients had clinically and/or pathologically documented extramedullary leukemia in additional sites such as CNS, breast, retina, gallbladder, soft tissue or pleura at some time during their clinical course. Among 10 patients with skin involvement at the time of diagnosis, six experienced a relapse involving the skin (skin alone, n = 5; skin and bone marrow, n = 1). In a study of 29 infants with AML, 13 had leukemia cutis.[13] Six of 13 were found to have extramedullary leukemia at diagnosis (CNS, n = 5; CNS and testis, n = 1). Eleven of these 13 infants with LC achieved a complete remission but seven relapsed sub-

sequently. None of these relapses occurred in the skin, but four involved the CNS.

The propensity of AML and LC to relapse in extramedullary sites after BMT may reflect unique biological properties of these leukemic cells. Although the molecular basis for the homing of hematopoietic cells to the bone marrow is not completely understood, several factors including expression of certain integrins have been shown to contribute to this process.[28] Recently, reduced expression of adhesion molecules on leukemic cells has been described in patients with CML[29,30] and CLL.[31] These abnormalities have been postulated to alter the homing of leukemic cells and to contribute to their independence of stromal cell support. Given their unusual propensity to seed and proliferate outside the marrow microenvironment, leukemic cells from patients with forms of AML associated with LC may exhibit the converse, namely an enhanced expression of adhesion molecules and/or a more stringent dependence on specific extramedullary microenvironmental influences for their growth and proliferation. Of particular interest in this regard would be studies of the expression of integrins and their putative homing ligands on leukemic cells of the M4 and M5 FAB morphology. In our series, 10 of 12 evaluable cases with leukemia cutis were of the FAB M4-M5 morphology at presentation. However, among evaluable patients without LC, 49 of 148 (33%) were also of this morphology. Strikingly, the risks of extramedullary relapse post-transplant in these two groups were 50% and 2% respectively, suggesting that determinants other than those distinguishing the M4-M5 morphologies contribute to a propensity for extramedullary seeding or growth.

In our study, the probability of skin relapse after BMT was 23% for patients with a previous history of LC. This high risk of skin relapse after BMT could reflect microscopic, subclinical foci of disease anteceding the transplant procedure. The addition of total skin electron beam radiation therapy (TSEBRT) has been proposed as one approach to this problem. Indeed, two case reports described successful treatment of recurrent AML with skin involvement by TSEBRT and chemotherapy.[14,32] However, the added toxicity of such an approach must be carefully considered, as severe skin toxicity has been reported in two patients treated with an anthracycline 2 and 12 days after completion of TSEBRT.[14,33] In our study, we did not observe any significant skin toxicity in two patients (UPN 254 and 320) who received a 400 cGy TSEBRT boost in addition to the hyperfractionated TBI regimen. Unfortunately, the antileukemic effects of this approach could not be evaluated in these two cases as one patient died from interstitial pneumonitis and the other patient relapsed with a chloroma of the breast 2 months post-transplant. One additional patient (UPN 1263), who had received 1800 cGy skin irradiation to his upper extremities 1 month before transplant, developed severe skin toxicity in the irradiated area after conditioning with busulfan, cyclophosphamide and cytarabine.

Chemotherapeutic regimens may also be effective in eradicating cutaneous sites of leukemia. For example, in the series of 13 infants with AML and LC reported by Pui *et al*[13] treated with standard AML chemotherapy using cytarabine, daunorubicin, and etoposide-based regimens without skin irradiation, none experienced a subsequent skin relapse. This suggests that adequate control of skin disease can be achieved with systemic chemotherapy. Modification of cytoreductive regimens to include agents which may better penetrate extramedullary sites may improve transplant results.

In conclusion, our study suggests that patients with AML receiving allogeneic marrow transplants who have a history of skin involvement differ markedly from other patients with AML transplanted at comparable stages of disease in their unique propensity to relapse in extramedullary sites. Further investigations are needed to understand the biological basis of this clinical feature and, thereby, to develop better strategies to either eradicate residual extramedullary sites of leukemia growth or prevent reseeding of leukemic cells in sites protected from the effector cells derived from a marrow allograft, that potentiate leukemic resistance.

Acknowledgements

This work was presented during the 36th annual meeting of the American Society of Hematology, December 2–6, 1994, Nashville, TN.

References

1 Long JC, Mihn MD. Multiple granulocytic tumors of the skin, report of six cases of myelogeneous leukemia with initial manifestations in the skin. *Cancer* 1977; **39**: 2004–2016.
2 Sun NCG, Ellis R. Granulocytic sarcoma of the skin. *Arch Dermatol* 1980; **116**: 800–802.
3 Neiman RS, Barcos M, Berard C *et al*. Granulocytic sarcoma: a clinicopathologic study of 61 biopsied cases. *Cancer* 1981; **48**: 1426–1437.
4 Su WPD, Buechner SA, Li CY. Clinicopathologic correlations in leukemia cutis. *Am Acad Dermatol* 1984; **11**: 121–128.
5 Meis JM, Butler JJ, Osbone BM, Manning JT. Granulocytic sarcoma in nonleukemic patients. *Cancer* 1986; **58**: 2697–2709.
6 Ohno S, Yokoo T, Ohta M *et al*. Aleukemic leukemia cutis. *J Am Acad Dermatol* 1990; **22**: 374–377.
7 Resnik KS, Brod BB. Leukemia cutis in congenital leukemia. Analysis and review of the world literature with report of an additional case. *Arch Dermatol* 1993; **129**: 1301–1306.
8 Su WPD. Clinical, histopathologic, and immunohistochemical correlations in leukemia cutis. *Semin Dermatol* 1994; **13**: 223–230.
9 Keating MJ, Freireich EJ. Acute myelogeneous leukemia. In: Bick RL (ed). *Hematology, Clinical and Laboratory Practice*. Mosby: St Louis, 1993, pp 1161–1195.
10 Boggs DR, Wintrobe MM, Cartwright GE. The acute leukemias: analysis of 322 cases and review of the literature. *Medicine* 1962; **41**: 163–225.
11 Byrd JC, Edenfield WJ, Shields DJ, Dawson NA. Extramedullary myeloid cell tumors in acute nonlymphocytic leukemia: a clinical review. *J Clin Oncol* 1995; **13**: 1800–1816.
12 Tobelem G, Jacquillat C, Chastang C *et al*. Acute monoblastic leukemia: a clinical and biological study of 74 cases. *Blood* 1980; **55**: 71–76.
13 Pui CH, Kalwinsky DK, Schell MJ *et al*. Acute nonlymphoblastic leukemia in infants: clinical presentation and outcome. *J Clin Oncol* 1988; **6**: 1008–1013.

14 Baer MR, Barcos M, Farrell H *et al*. Acute myelogeneous leukemia with leukemia cutis. Eighteen cases seen between 1969 and 1986. *Cancer* 1989; **63**: 2192–2200.
15 Thompson CB, Sanders JE, Flournoy N *et al*. The risk of central nervous system relapse and leukoencephalopathy in patients receiving marrow transplants for acute leukemia. *Blood* 1986; **67**: 195–199.
16 Sanders JE, Flournoy N, Thomas E *et al*. Marrow transplant experience in children with acute lymphoblastic leukemia: an analysis of factors associated with survival, relapse and graft-versus-host disease. *Med Ped Oncol* 1985; **13**: 165–172.
17 Shank B, Hopfan S, Kim JH *et al*. Hyperfractionated total body irradiation for bone marrow transplantation: early results in leukemia patients. *Int J Radiat Oncol Biol Phys* 1981; **7**: 1109–1115.
18 Young JW, Papadopoulos EB, Cunningham I *et al*. T-cell depleted allogeneic bone marrow transplantation in adults with nonlymphocytic leukemia in first remission. *Blood* 1992; **79**: 3380–3387.
19 Papadopoulos EB, Carabasi M, Young J *et al*. Results of T-cell depleted (TCD) allogeneic BMT after TBI, thiotepa and cyclophosphamide in patients with leukemia. *Blood* 1992; **80** (Suppl. 1): 170a.
20 Papadopoulos EB, Caron P, Castro-Malaspina H *et al*. Results of allogeneic bone marrow transplant following ^{131}I-M195/busulfan/cyclophosphamide in patients with advanced/refractory myeloid malignancies. *Blood* 1993; **82** (Suppl. 1): 80a.
21 Reisner Y, Kapoor N, Kirkpatrick D *et al*. Transplantation for severe combined immunodeficiency with HLA-A, B, D, DR incompatible parental marrow cells fractionated by soybean agglutinin and sheep red blood cells. *Blood* 1983; **61**: 341–348.
22 Reisner Y, Kirkpatrick D, Dupont B *et al*. Transplantation for acute leukemia with HLA-A and B nonidentical parental marrow cells fractionated with soybean agglutinin and sheep red blood cells. *Lancet* 1981; **2**: 327–331.
23 Glucksberg H, Storb R, Fefer A *et al*. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HLA-matched sibling donors. *Transplantation* 1974; **18**: 295–304.
24 Shulman HM, Sullivan KM, Weiden PL *et al*. Chronic graft-versus-host syndrome in man: a long-term clinico-pathologic study of 20 Seattle patients. *Am J Med* 1980; **69**: 204–217.
25 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–481.
26 Kalbfleisch JD, Prenctice RL. *The Statistical Analysis of Failure Time Data*. Wiley: New York, NY, 1980, p 163.
27 Wilcoxon F. Individual comparisons by ranking methods. *Biometrics*, 1945; **1**: 80–83.
28 Tavassoli M, Hardy CL. Molecular basis of homing of intravenously transplanted stem cells to the marrow. *Blood* 1990; **76**: 1059–1070.
29 Lanza F, Bi S, Castoldi G, Goldman JM. Abnormal expression of N-CAM (CD56) adhesion molecule on myeloid and progenitor cells from chronic myeloid leukemia. *Leukemia* 1993; **7**: 1570–1575.
30 Verfaillie CM, McCarthy JB, McGlave PB. Mechanisms underlying abnormal trafficking of malignant progenitors in chronic myelogenous leukemia. *J Clin Invest* 1992; **90**: 1232–1241.
31 De Rossi G, Zarcone D, Mauro F *et al*. Adhesion molecule expression on B-cell chronic lymphocytic leukemia cell phenotypes defines distinct disease subsets. *Blood* 1993; **81**: 2679–2687.
32 Rubin CM, Arthur DC, Meyers G *et al*. Leukemia cutis treated with total skin irradiation. *Cancer* 1984; **55**: 2649–2652.
33 Solberg LA, Wick MR, Bruckman JE. Doxorubicin enhanced skin reaction after whole-body electron beam irradiation for leukemia cutis. *Mayo Clin Proc* 1980; **55**: 711–715.