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ALLOGENEIC BONE MARROW TRANSPLANTATION IN LEUKEMIA

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Abstract

This paper describes European experience of bone marrow transplantation for hematological malignancies. From 1979 until December 1986 2224 transplants were reported to the European registry. The results clearly show that the leukemia-free survival is highest when the transplant is performed in the first complete remission of acute leukemia or in the first chronic phase of chronic myeloid leukemia. Under these conditions 50% of the patients can be expected to be alive and well at 8 years after the transplantation. Other factors influencing leukemia-free survival are age, donor-recipient sex combination, and prevention of graft-versus-host disease with cyclosporine.

Key words: Leukemia, allogeneic bone marrow transplant, prognostic factors.

Bone marrow transplantation has been used in Europe during the last decade for the treatment of hematological malignancies with increasing success and with a steadily increasing frequency. This retrospective analysis of the combined European results since 1979 allows a description of the changes in patient selection, conditioning and graft-versus-host disease (GvHD) prevention. It documents the major factors influencing the final outcome of the transplant.

Material and Methods

The Working Party Leukemia of the European cooperative group for bone marrow transplantation (EBMT) has been collecting data from European Centers since 1979. Information on age and sex of patient and donor, diagnosis and stage of the disease, date of the transplantation, details of the conditioning regimen, GvHD prophylaxis, complications and final outcome is obtained from each center for every individual patient by questionnaire. Questionnaires are distributed annually or biannually. Information on surviving patients is updated every year. All consecutive transplants should be reported by every center for patients transplanted in remission of acute leukemia or in chronic or accelerated phase of chronic myeloid leukemia.

The EBMT data base now includes a total of 2224 reported allogeneic or syngeneic transplantations performed in Europe for hematological malignancies between 1975 and 1986. There were 803 patients transplanted for acute myeloid leukemia (AML), 703 for acute lymphocytic leukemia (ALL), 672 for chronic myeloid leukemia (CML) and 46 for other hematological diseases. Of the transplants 2020 derived from an HLA-identical sibling donor, 67 from an identical twin, 17 from an identical related donor, 98 from an haplo-identical related donor, 5 from a haplo-identical unrelated donor and 7 from an identical unrelated donor. In 10 patients details were missing. Quality control of the data base showed less than 1% obvious errors.

In a first analysis we were interested in the changes over time in the patient population, the changes in methods of GvHD prevention and irradiation strategy. For this purpose cohorts were formed according to the year of transplantation (–1980, 1981–1984, 1985–1986).

In a second analysis the evaluation was restricted to patients with AML, ALL and CML receiving a transplant from an HLA-identical sibling donor. For a multivariate analysis of leukemia risk factors influencing leukemia-free survival and transplant-related mortality, the patients were grouped into 4 cohorts (Table), according to the factors which were previously found to be significant in univariate analysis: remission status, age of the patient, GvHD prevention and donor-recipient sex combination.

Remission status was divided into good risk, including AML first complete remission (CR), ALL first complete

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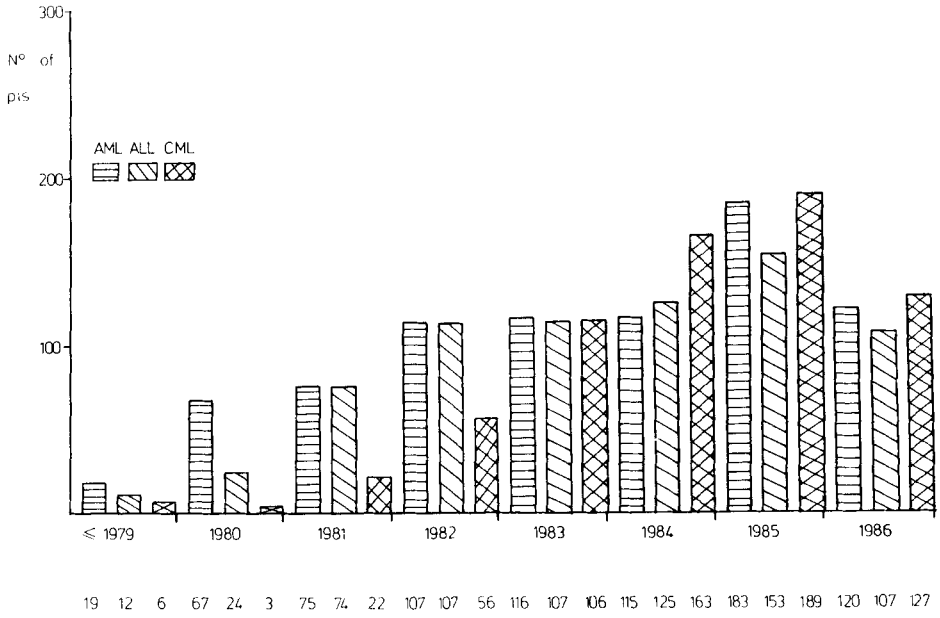

Fig. 1. Diagnostic categories by calendar year.

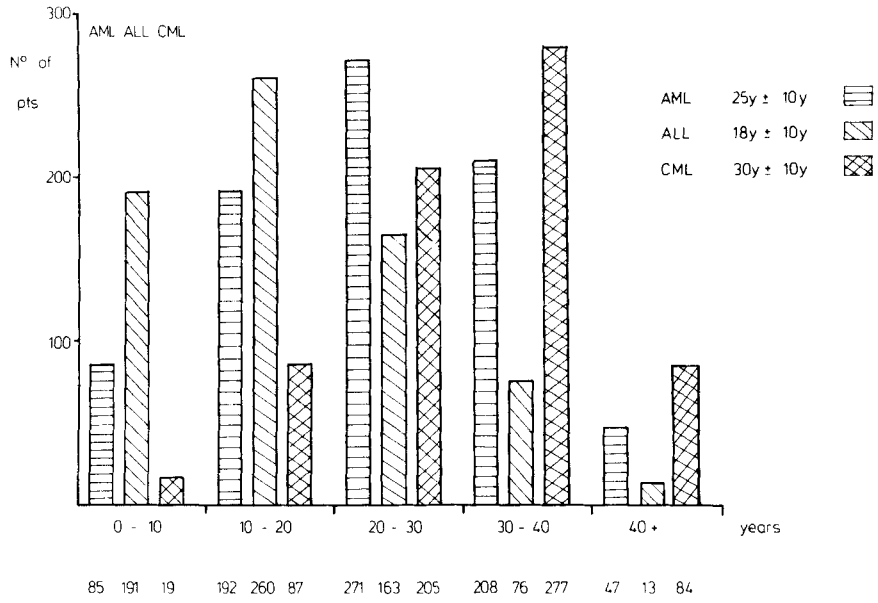

Fig. 2. Distribution of diagnostic categories in different age groups.

remission, CML first chronic phase (CP) and bad risk, which included all patients not fulfilling the good risk criteria. Age was grouped by decades. GvHD-prevention was divided into 3 groups: cyclosporine as sole method for GvHD prevention, cyclosporine combined with any other method, e.g. methotrexate, prednisone and T-cell depletion and no cyclosporine. This last group includes patients treated with methotrexate, prednisone, T-cell depletion or given no GvHD-prevention at all.

These groups were analysed by cross-tabulations for differences of the variables within the cohorts and for changes over time and by diagnostic category. Cross-tabulations were compared by the Chi-square test, survival was analyzed according to the method of Kaplan & Meier and differences between survivals were studied with the Lee-Desu test. The Cox regression model was used to compare the parameters involved in a multivariate analysis.

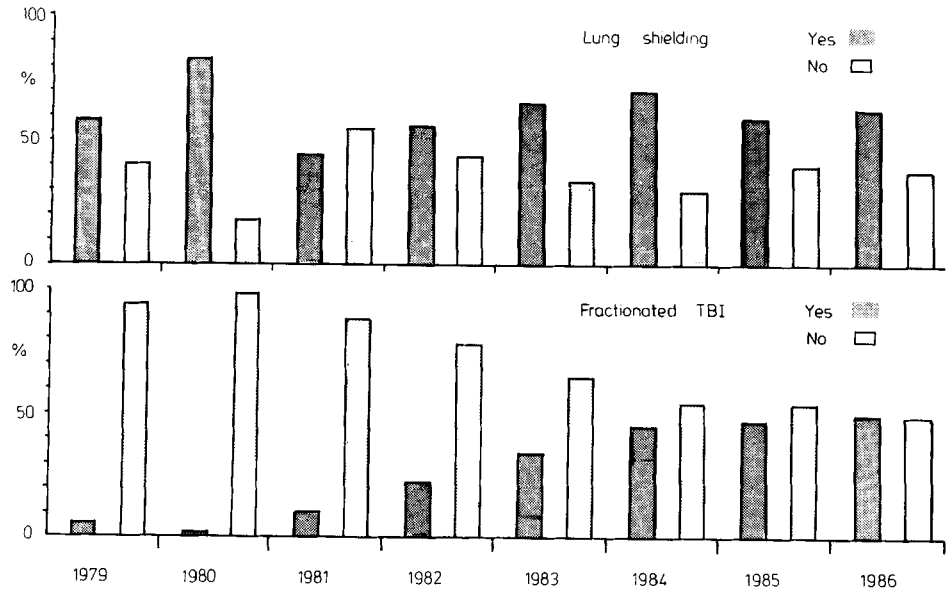

Fig. 3. Changes in lung-shielding and in fractionation of total body irradiation.

Table

Cohorts selected for the multivariate analysis

1. Remission status (CR = complete remission; cP = chronic phase)		
Good risk: (n=1292)	AML 1st CR 578, ALL 1st CR 260, CML 1st cP 454	
Bad risk: (n=661)	AML not 1st CR 149, ALL not 1st CR 360, CML not 1st cP 152	
2. Age		
0–10 years	249	
11–20 years	467	
21–30 years	590	
31–40 years	521	
>41 years	130	
3. Method for prevention of graft-versus-host disease		
Cyclosporine alone	684	
Cyclosporine plus others	356	
No cyclosporine	917	
4. Donor-recipient sex combination		
Recipient male, donor male		632
Recipient male, donor female		484
Recipient female, donor male		439
Recipient female, donor female		400

Results

There had been clear changes in the patient population since the introduction of the EBMT registry in 1979. Until 1982, AML and ALL were the main diagnostic categories. Since 1981 a continuous increase had been seen in transplantations for CML, and in 1985 and 1986 CML was the most frequent indication for an allogeneic transplant (Fig. 1). Since the distribution of the 3 diseases by age is inhomogenous, the median age of the patients transplanted has steadily increased (Fig. 2). The most frequent conditioning regimen is still cyclophosphamide and total body irradiation (TBI). There is a controversy about the best irradiation modality. Lung-shielding is used in about 60% of the patients with no clear trend. Single dose TBI was most frequently used in 1979, but in 1986 single dose and fractionated TBI became evenly distributed (Fig. 3). Similarly, the optimal GvHD prevention remains a matter of debate. In 1979 methotrexate was the standard GvHD prevention. Cyclosporine with or without methotrexate and T-cell depletion with or without additional intervention were used in 1986 (Fig. 4).

The probability of the leukemia-free survival for all transplanted patients with leukemia is shown in Fig. 5. Of all patients 38% could be expected to be alive and well 7 years after transplantation. The first major factor influencing outcome was the stage of the disease as shown in Fig. 6. Independent of the diagnostic category, AML, ALL or CML, survival was 50% if the transplantation was performed in first complete remission or in chronic phase of CML, compared to 30% if the transplant was performed at a later stage of the disease. Survival was influenced by the method of GvHD prevention. As an independent factor, cyclosporine influenced leukemia-free survival and transplant-related mortality in AML and ALL patients but is not significant in CML patients (Fig. 7). These factors can be influenced by the referring physicians or by the transplantation teams. Additional factors influencing outcome were age of the patient, as exemplified in Fig. 9, showing the increase of transplant-related mortality decade by decade with a marked increase above the age of 20 years. The donor-recipient sex combination was an important factor. A female donor for a male recipient increased the risk of transplant-related mortality,

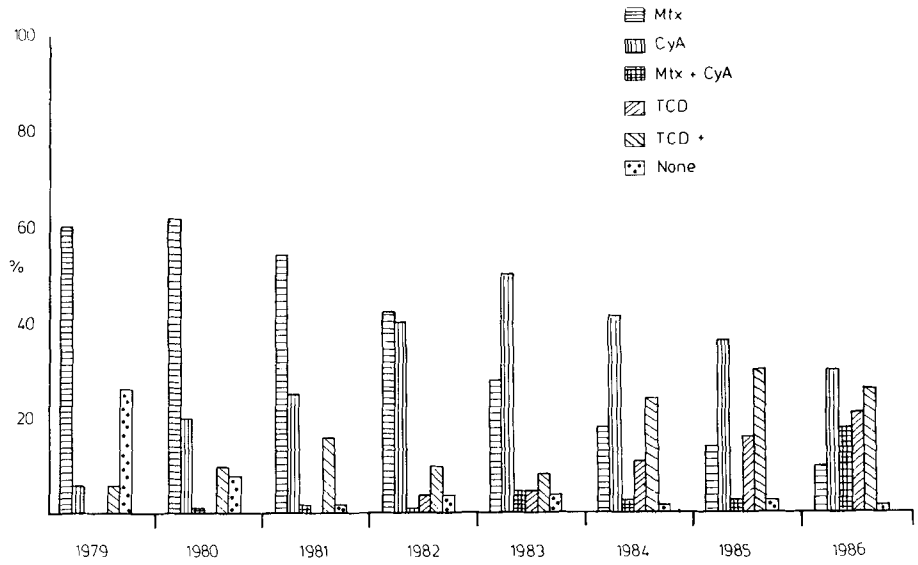

Fig. 4. GvHD prevention method by calendar year.

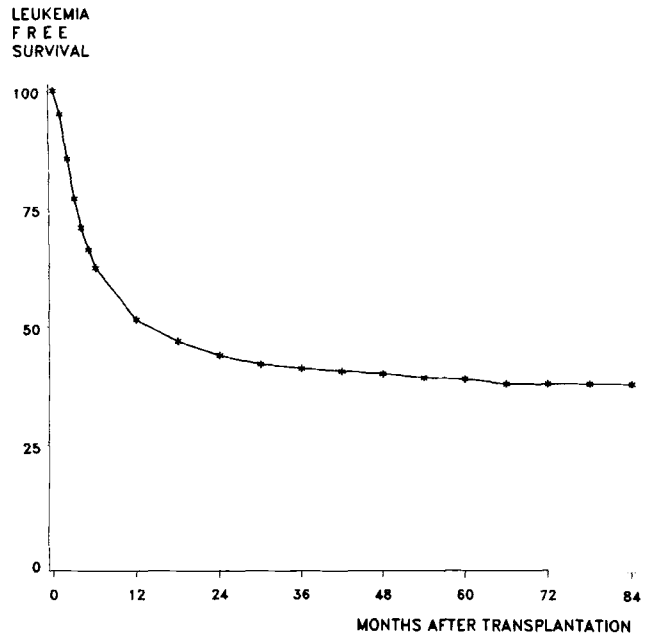

Fig. 5. Leukemia-free survival (months after transplantation) for all 2224 EBMT patients.

graft-versus-host disease and pneumonitis, while a female donor for a female recipient reduced these risks. A male donor neither increased nor reduced the risks to male or female recipients (Fig. 8). These results were not influenced by the centers or by the center size and have remained basically the same since the introduction of the registry in 1979 (Fig. 10).

Discussion

The results of this analysis are descriptive and clear. There have been changes in the last 6 years. CML, a rare indication in 1980, is now the most frequent indication and new, other hematological malignancies, such as myelodysplastic syndromes and chronic lymphocytic leukemia,

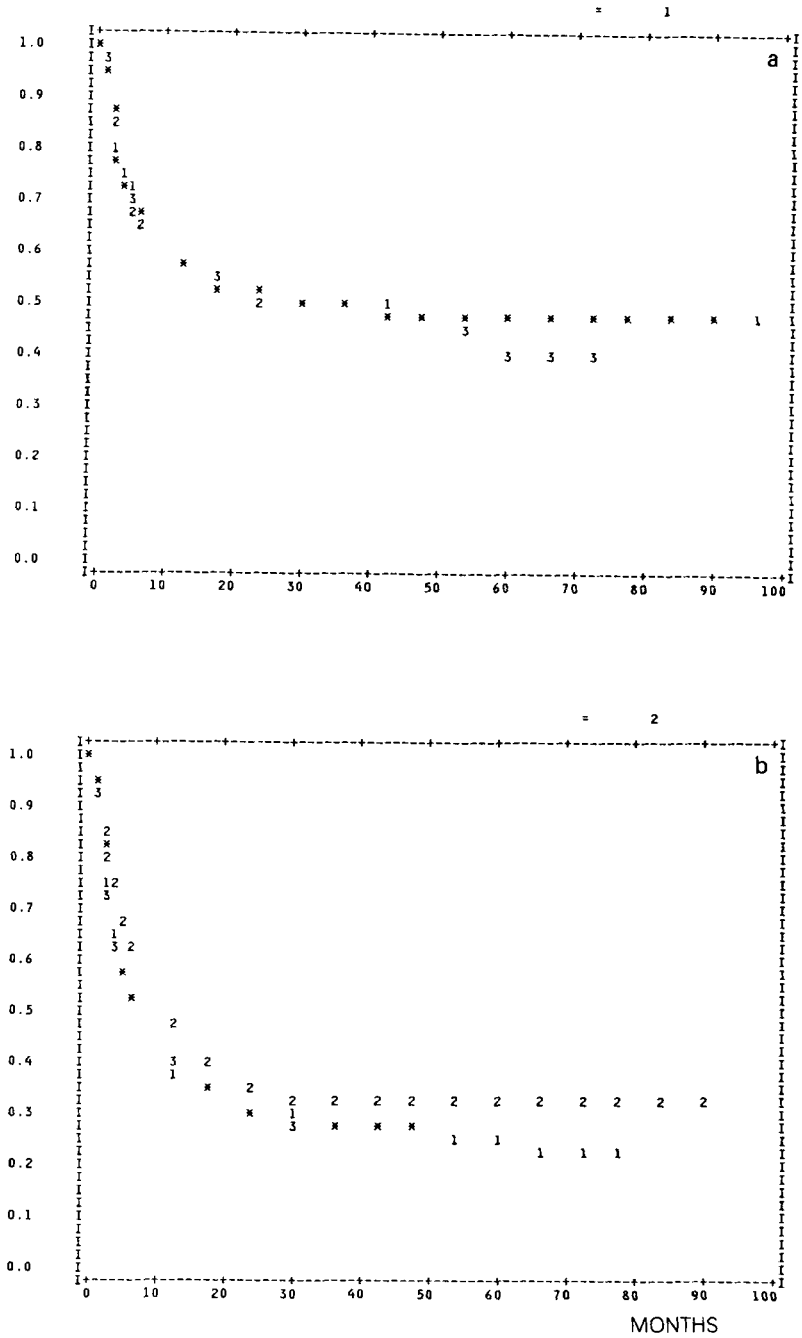

Fig. 6. Leukemia-free survival depending on the diagnostic category: a) First remission of acute leukemia or first chronic phase of chronic myeloid leukemia. b) Other stages of acute leukemia or accelerated phase of chronic myeloid leukemia. 1=acute myeloid leukemia, 2=acute lymphocytic leukemia, 3=chronic myeloid leukemia, x=1+2 or 2+3 or 1+2+3.

are emerging. There is a trend to transplant older patients despite the clear increase in transplant-related mortality by age. There is still no ideal conditioning, no ideal irradiation regimen and no ideal graft-versus-host-disease prevention.

The observation of factors influencing leukemia-free survival and transplant-related mortality is important. Stage of the disease, age of the patient, donor-recipient sex combination and the use of cyclosporine for graft-versus-host disease prevention are all important prognostic factors. Outcome is not influenced by the diagnosis and has not improved during the last 8 years. The last mentioned facts may indicate that the different leukemias could represent basically the same disease and that the

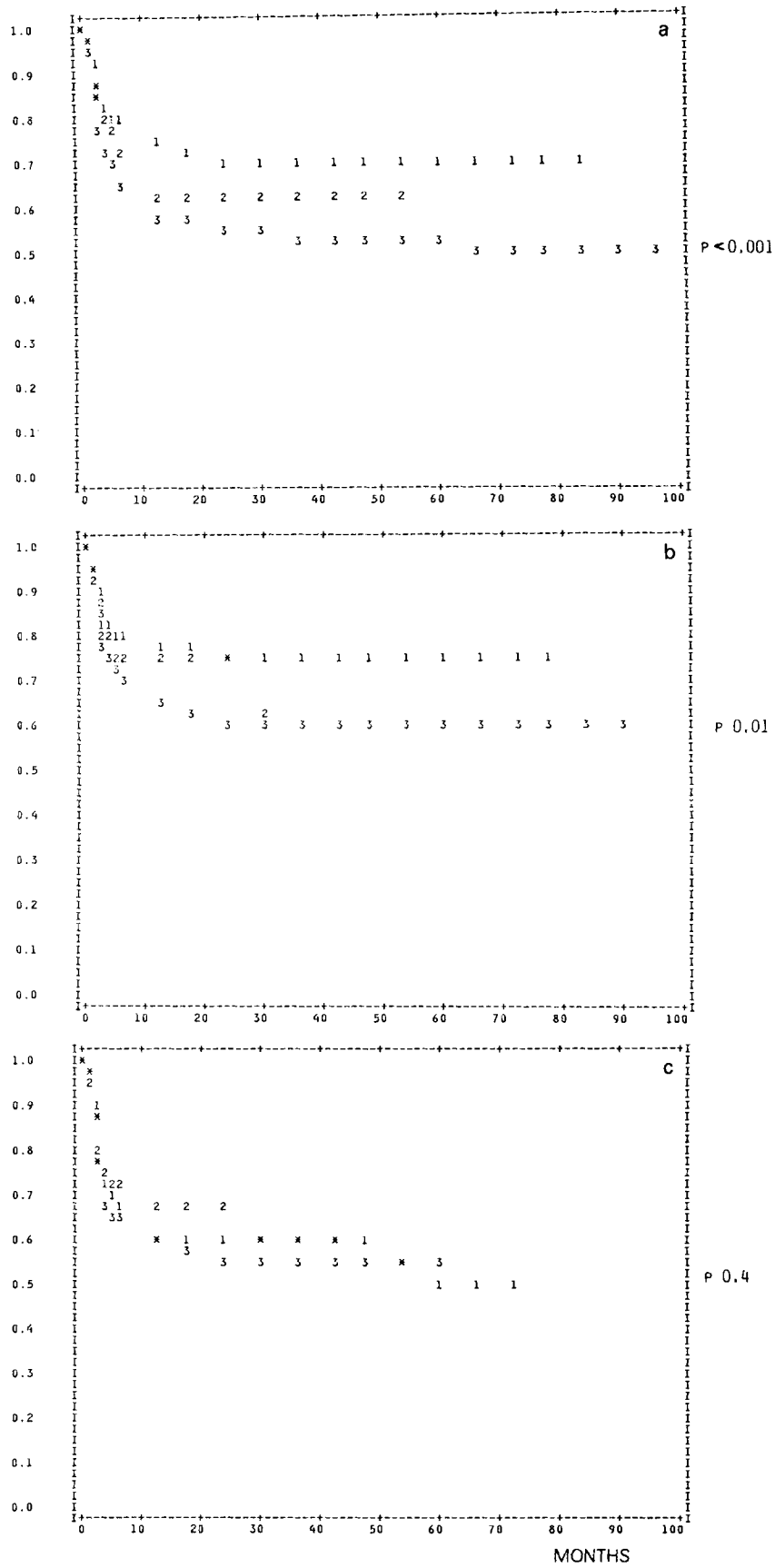

Fig. 7. Influence of graft-versus-host-disease prevention on leukemia-free survival in a) acute myeloid leukemia, b) acute lymphocytic leukemia and c) chronic myeloid leukemia. 1=prevention with cyclosporine alone, 2=prevention with cyclosporine in combination (see text), 3=prevention without cyclosporine (see text). x=1+2 or 2+3 or 1+2+3.

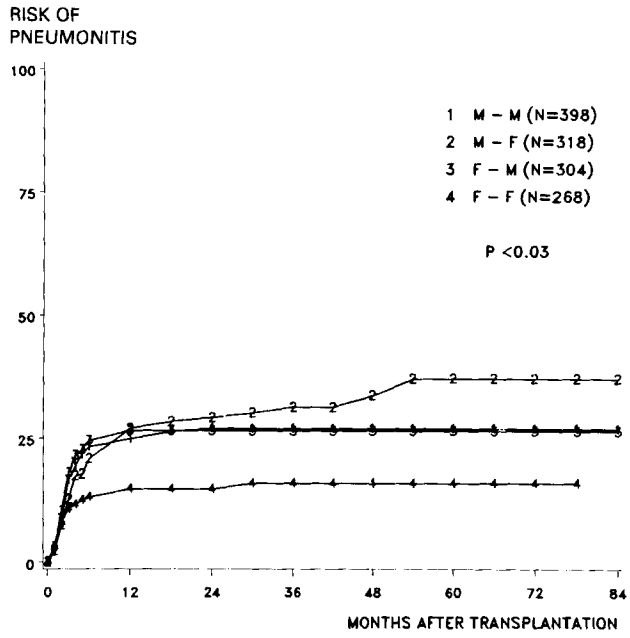

Fig. 8. Influence of donor-recipient sex combination on interstitial pneumonitis.

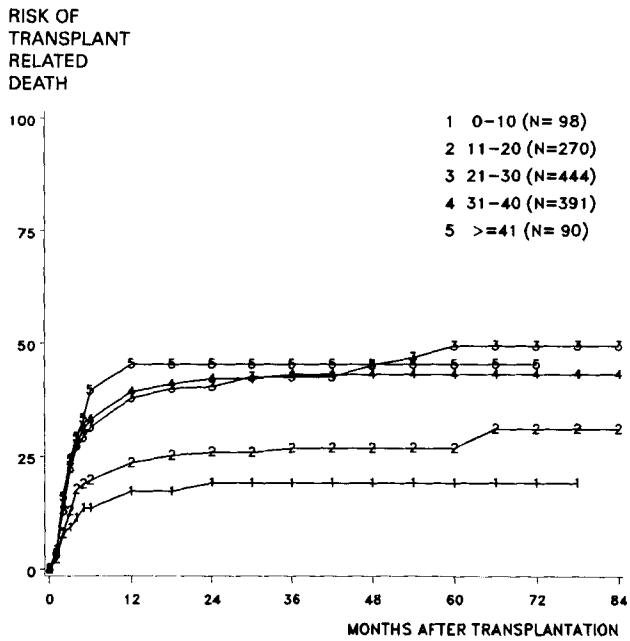

Fig. 9. Transplant-related mortality by age.

major important factor for cure of any leukemia is the effect of the allogeneic bone marrow. If we could better exploit this effect we could improve the treatment of hematological malignancies.

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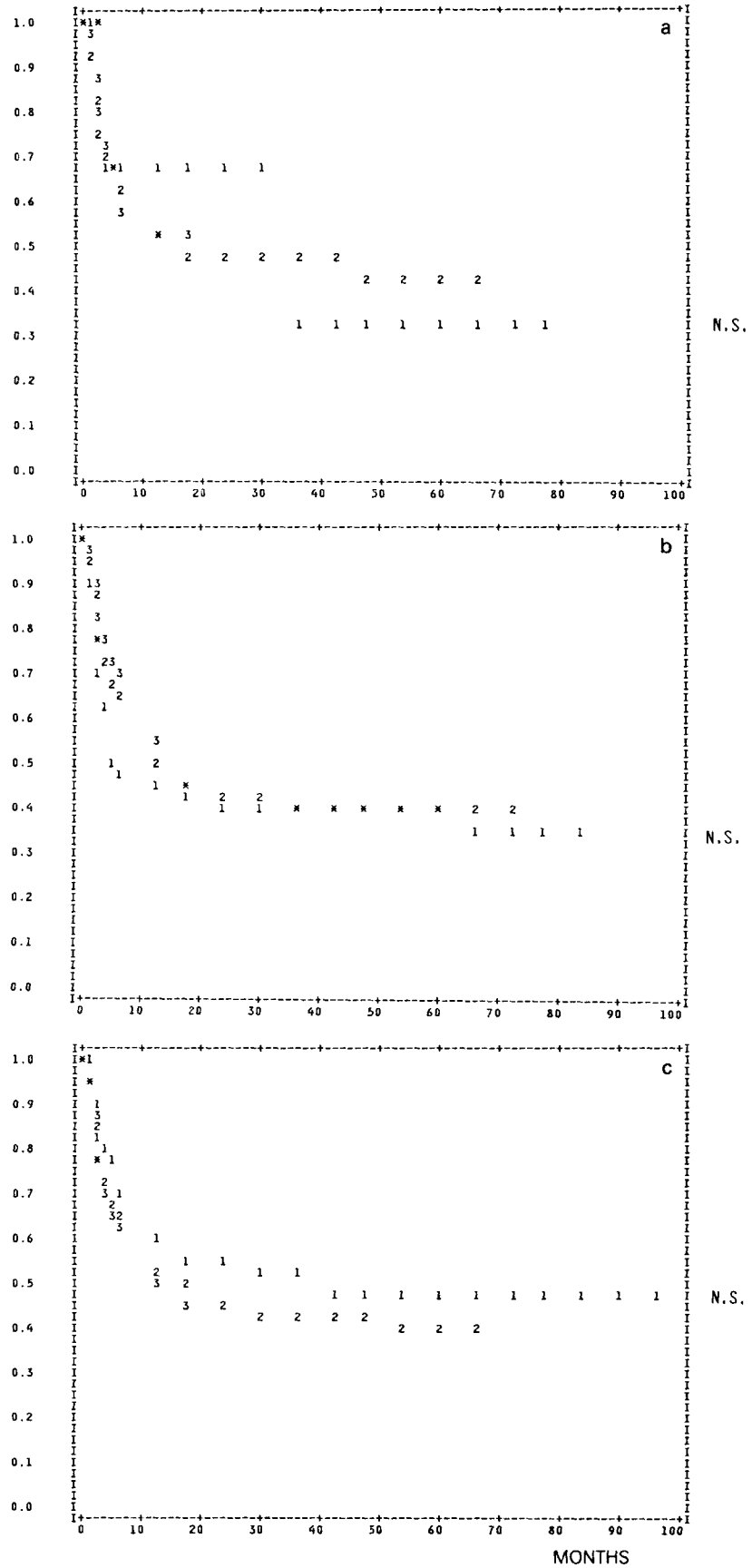

Fig. 10. Leukemia-free survival depending on center size and year of the transplant. a). Centers with less than 20 transplants. b). Centers with 20–75 transplants. c). Centers with more than 75 transplants. 1=transplants received before or in 1980, 2=transplants received 1981–1984, 3=transplants received in 1985–1986, x=1+2 or 2+3 or 1+2+3.

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