Haematology and Blood Transfusion Vol. 28
Modern Trends in Human Leukemia V
Edited by Neth, Gallo, Greaves, Moore, Winkler

Bone Marrow Transplantation in West Germany in Patients with Leukemia *

K. Wilms, K. Schüch, C. Müller, H. Link, P. Meyer, P. Ostendorf, H. D. Waller, P. Wernet, D. Niethammer, H. Dopfer, W. Schneider, F. Schunter, G. Breitling, W. Frommhold, G. Seeger, A. C. Voss, and H. Rodt

A. Introduction

Bone marrow transplantations (BMT) are being performed in West Germany, the United States, and other European countries with increasing frequency. The first allogeneic BMT in Germany was done in Munich 1975 in a patient with severe aplastic anemia. Since then 128 BMTs have been registered by the German Group for BMT, which consists of four active transplantation centers: Essen, Munich, Tübingen, and Ulm. All these transplantation units are not independent institutions, but are integrated into medical or pediatric departments of university hospitals. Thus all groups treat patients with hematological neoplasias or bone marrow failure in the conventional way as well.

The German Group for BMT organizes regular plenary meetings, stimulates common study protocols, and organizes the assignment of patients from one center to another according to actual capacity. We present the Tübingen experience here, with discussion of the clinical management, results, and experimental approaches.

B. Patients and Methods

Thirty-three BMTs were performed in Tübingen between August 1976 and May 1982. Seven patients suffered from severe aplastic anemia, 25 patients were transplanted for acute leukemia, and one patient was transplanted for chronic myelocytic leukemia in the chronic phase. The first three leukemia patients transplanted in Tübingen in 1976/1977 were in the end stage of their disease and resistant to conventional chemotherapy. All patients died in the early posttransplant period from persisting leukemia or leukemia-related complications. In October 1979 we decided, as the first group in Germany, to perform BMT in patients with leukemia only in remission. This decision was based on the Seattle experience with this procedure [5, 6]. Since that time we have transplanted 22 leukemic patients in remission. Diagnoses and remission status are shown in Table 1.

The age range of the patients was between 3 and 35 years. The donors were identical twins in two cases; the others were siblings with HLA-A, B, C, D and D_R identity, with one exception, a positive MLC. In eight cases there was an ABO incompatibility, requiring a plasma exchange in one case with a very high isoagglutinin titer; in the other cases buffy coat preparations were grafted. All patients were

Table 1. Bone marrow transplantation in patients with leukemia in remission ($n=22$). Diagnoses and remission status

	I.	II.	III.	remission
AML	6	6	1	
ALL		5	2	
AUL	1			
CML	1 (chronic phase)			

* With the support of the Deutsche Forschungsgemeinschaft, DFG Forschergruppe „Leukämieforschung", Wa 139/11-139/13-5

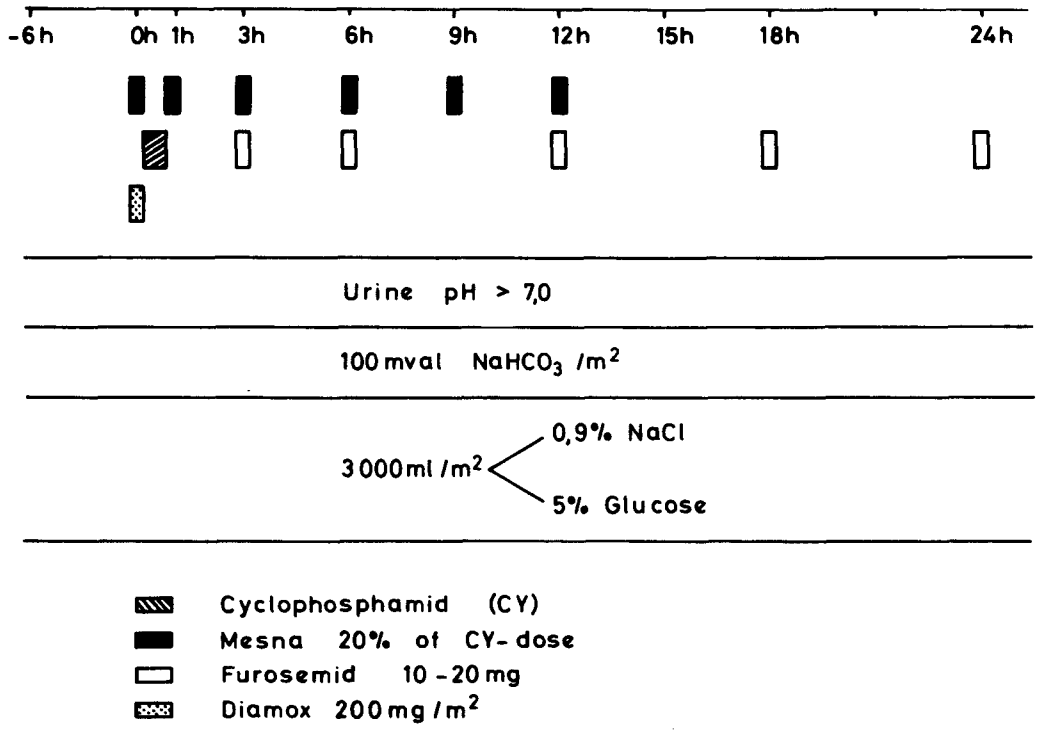

Fig. 1. Protocol for uroprotection with Mesna to prevent cyclophosphamide-induced cystitis

treated under gnotobiotic conditions in Laminar airflow units and received Bactrim prophylaxis for pneumocystis. The conditioning regimen consisted of 60 mg/kg cyclophosphamide on days −5 and −4. Under strict uroprotection with Mesna, according to the protocol outlined in Fig. 1, with shortened application intervals [1] no hematuria occurred.

Total body irradiation was performed on day 0 before marrow infusion, with a 10-MeV linear accelerator at a dose rate of 0.07 Gy/min up to a midline dose of 10 Gy. The lung dose was limited to 8 Gy by satellite technique. Patient No. 16 received a fractionated irradiation with 7×2 Gy on consecutive days. The bone marrow aspiration was performed according to the technique of Thomas and Storb [4]. In our first marrow transplantation we were impressed by striking megaloblastic abnormalities in the newly engrafted marrow, independent of methotrexate. We found severely decreased levels of folic acid in the early posttransplant phase in spite of regular oral substitution, presumably due to diminished absorption caused by the radiation-induced damage to the intestine in the light of the low storage capacity for this vitamin. In view of this experience we give a consequent intravenous substitution of folic acid as a part of our hyperalimentation protocol.

GvHD Prophylaxis by Preincubation with AHTCG

In addition to this general procedure we have investigated in Tübingen, in close cooperation with the Munich group of Drs. Thierfelder and Rodt, the prophylaxis of graft-versus-host-disease (GvHD) by preincubation of the aspirated marrow suspension with rabbit anti-human-T-cell-globulin (AHTCG) for depletion of GvH reactive cells before the marrow infusion. The experimental data and the theoretical background have been published by the Munich group [3].

Until May 1982 we performed this preincubation in 17 patients. The methotrexate regimen was carried out after the marrow graft in the usual way.

C. Results

The patient characteristics and clinical outcome of 22 leukemic patients transplanted in remission can be seen from Table 2. All patients had a documented take. There were no serious complications in the early

Table 2. Clinical data, course, and present status of 22 leukemia patients transplanted in remission

Pat. No.	Age (years)/ sex	Diagnosis remission	Blood group of patient/ donor	Marrow incubation with ATCG +/–	GvH Acute/chronic Grade		Complications	Cause of death	Survival in days from 31.5.82
7	11 M	ALL 2nd	A/A	–	twins		MTX leukencephalopathia		961
8	6 M	AML 2nd	0/0	+	I/II°		Relapse day 691 testes		919
10	19 F	AUL 1st	0/0	+			Interstitial pneumonia	Interstitial pneumonia	65 †
11	25 F	AML 1st	B/0	+	I°	II°	Bronchopneumonia, herpes zoster gen.	Herpes zoster pneumonia cGvH	213 †
12	27 F	AML 1st	A/A	+	I/II°	II/III°	Obstruct. ventil. disorder, bronchopneumonia, herpes simplex stomatitis	CMV, pneumonia cGvH	420 †
14	12 F	AML 2nd	A/A	+			Candida pneumonia, zoster segm., pericardial effusion		592
16	9 M	ALL 3rd	A/0	+	I°	II°	Pulmonary aspergillus, herpes zoster segm.	Lung bleeding	312 †
17	16 M	AML 1st	A/B	+			Interstitial pneumonia	Interstitial pneumonia	33 †
18	3 M	ALL 2nd	A/0	+	I°				392
19	29 M	AML 1st	A/A	–		III°	CMV hepatitis		377
20	14 F	ALL 2nd	A/A	–	twins				338
21	35 M	AML 2nd	A/A	+			Relapse day 112, pulmonary aspergillus	Cerebral hemorraghia	123 †
22	10 M	ALL 2nd	0/0	+	I°				268
23	34 M	AML 2nd	0/A	–			Interstitial pneumonia	Interstitial pneumonia	86 †
24	17 M	AML 2nd	0/B	+					205
25	17 M	ALL 3rd	0/A	–	III°	III°	cGvH and liver insufficiency	Sepsis cGvH	78 †
26	21 M	AML 1st	A/0	+	III°	II°	cGvH and liver insufficiency, herpes simplex stomatitis		93 †
27	26 F	AML 1st	A/0	+					135
28	15 F	CML chronic phase	0/0	+					114
29	24 F	AML 3rd	B/B		I°	I°	Hepatitis (?)		86
30	20 F	AML 2nd	A/A				Hepatitis B, herpes simplex stomatitis		44
32	25 F	ALL 2nd	0/0						9

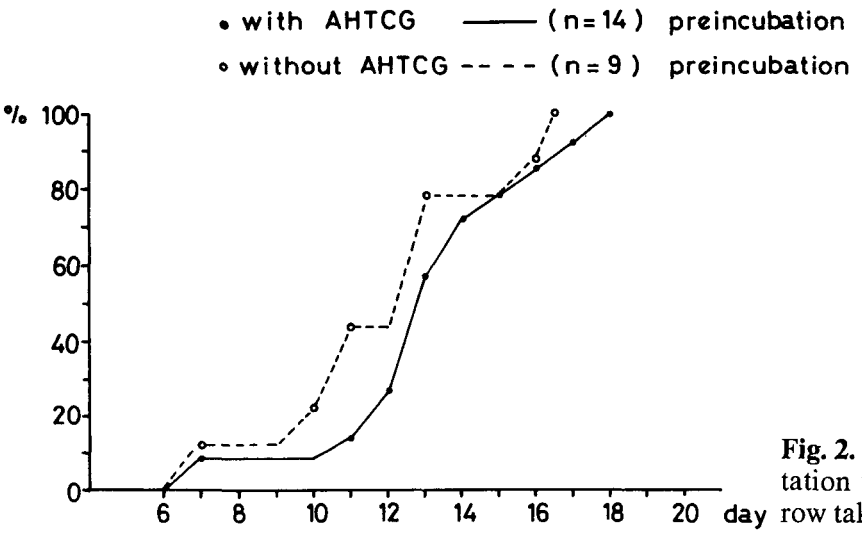

Fig. 2. Time interval from transplantation to documentation of bone marrow take

posttransplant period or deaths related to the transplant procedure. No interference of the AHTCG preincubation with the bone marrow take was observed (Fig. 2). In the later posttransplant period nine patients have died so far. The actuarial survival rate after 1 year is 55%. Major complications were infections, chronic GvHD, and a combination of both. The causes leading to death in these nine patients can be seen in Table 3. Only two out of 21 patients had a leukemic relapse more than 50 days posttransplant. Patient No. 8 developed a testicular relapse on day 691. In patient No. 21, who was transplanted for AML in second remission after rather short duration of the first remission, rapidly progressing bone marrow failure was the first evidence for a relapse, which was diagnosed on day 112. The patient died in overt leukemia from cerebral hemorrhage.

Acute GvHD was not a major clinical problem. We assume that this was due to the AHTCG preincubation: Out of the 16 patients at risk, only one, who was grafted with preincubated marrow cells, had a clinical relevant acute GvHD (grade 3). A transient skin rash with later slight increase in liver enzymes and without intestinal symptoms was observed in 8 out of the 16 patients at risk.

Table 3. Causes of death after allogeneic bone marrow transplantation in patients with leukemia in remission (9/22 patients)

	n
Chron. GvHD with infectious complications	5
Interstitial pneumonia	2
Viral encephalitis	1
Leukemic relapse	1

In contrast major problems were caused in our series by chronic GvHD. We observed this syndrome in six patients, in five after engraftment of preincubation marrow. We were able to favorably influence the clinical symptoms by prednisolone/azathioprine treatment, but five patients with chronic GvHD died from infectious complications due to the severe immunodeficiency caused by this disease. Of particular interest was an obstructive ventilation disorder which occurred in two patients after the onset of chronic GvHD. Treatment with corticosteroids, antibiotics, and adequate broncholytic measures did not prevent progression. Both patients developed recurrent pneumothorax as a later complication. Progressive respiratory failure and subsequent overwhelming infections were fatal in both cases. Interstitial pneumonia as typical complication in the later posttransplant period occurred in five patients, in only two cases without association of chronic GvHD. This was due to cytomegalovirus and varicella-zoster virus respectively and of an unidentified etiology in three cases.

We conclude from our experience that preincubation with the Munich AHTCG reduces morbidity and mortality of acute GvHD but does not prevent chronic GvHD. So in our opinion it is a logical consequence to combine this procedure

with other methods to control immune reactions or induce tolerance. In this direction we have initiated a protocol to combine AHTCG preincubation with cyclosporin A treatment.

In the context of these objectives of improving the control of the potentially life-threatening GvH reaction, improvement of the diagnostic tools and a better pathophysiological understanding of this condition are important. Since 2 years Müller in our group has been supplementing the histological estimation carried out by F. R. Krüger (Cologne) by immunohistological analysis with monoclonal antibodies [2]. It is too early to draw definite conclusions, but the preliminary results can be summarized insofar that in GvH reactions lymphoid infiltrates consist of mature T cells, that there is a focal or generalized appearance of Ia-like antigens on keratinocytes, and that there is a partial reduction of Langerhans cells.

D. Conclusion

The impact of BMT on the treatment of acute leukemias and chronic myelocytic leukemia cannot yet be estimated definitely. We think that with the increased rate of complete remissions in adult AML by the improvement of induction regimens in the past years and the limited results in conventional maintenance therapy for remaining in continuous remission, BMT in first remission should be considered a treatment strategy with curative potential in patients with histocompatible sibling donors under the age of 35 years. In a common protocol with the Ulm group we treat our AML patients according to a regimen which integrates BMT for those patients with an available donor (Fig. 3). This protocol has also been taken up by other non transplanting members of the South German Hemoblastosis Group. In ALL we recommend transplantation in adults still in second remission in addition to high-risk patients.

The indication for BMT in children has been widely discussed in the German BFM Study Group, with the conclusion that transplantation in AML in first remission is not generally acceptable. Children with ALL, besides rare cases of B-ALL, should be transplanted in second remission. In CML in adults and children risk factors must be evaluated for an individual decision.

The four German centers have an annual transplantation capacity now of about 10–15 each. Two other groups are in preparation. The future will show if this capacity is sufficient when, we hope, favorable long-term results are produced and the potential complications of GvHD and interstitial pneumonia can be prevented or treated effectively.

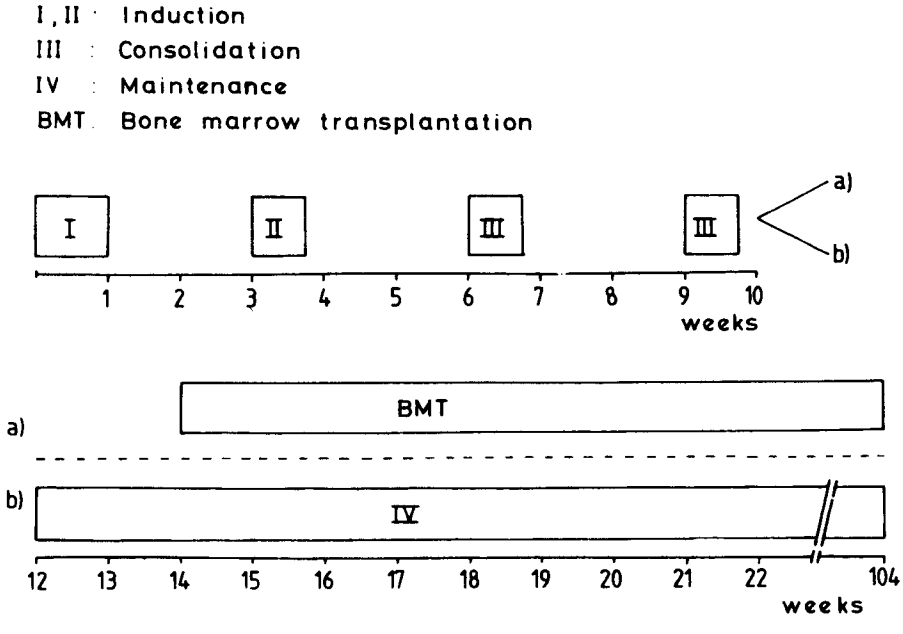

Fig. 3. Schematic outline of the present protocol for adult patients with acute nonlymphoblastic leukemia achieving complete remission

References

1. Link H, Neff V, Niethammer D, Wilms K (1981) Prophylaxis of hemorrhagic cystitis due to cyclophosphamide-conditioning for bone marrow transplantation. Blut 43:329
2. Müller C, Schüch K, Pawelec G, Wilms K, Wernet P (1982) Immunohistology of graft-versus-host disease mediated skin lesions and its correlation to a large granular lymphocyte surface phenotype and function. Blut 44:89
3. Rodt H, Kolb HJ, Netzel B, Rieder I, Janka G, Belohradsky B, Haas RJ, Thierfelder S (1979) GvHD suppression by incubation of bone marrow grafts with anti-T-cell globulin: effect in the canine model and application to clinical marrow transplantation. Transplant Proc 11:962
4. Thomas ED, Storb R (1970) Technique for human marrow grafting. Blood 36:507
5. Thomas ED, Buckner CD, Clift RA, Fefer A, Johnson FL, Neiman PE, Sale GS, Sanders JE, Singer JW, Shulman H, Storb R, Weiden P (1979) Marrow transplantation for acute nonlymphocytic leukemia in first remission. N Engl J Med 301:597
6. Thomas ED, Sanders JE, Flornoy N, Johnson FL, Buckner CD, Clift RA, Fefer A, Goodwell BW, Storb R, Weiden P (1979) Marrow transplantation for patients with acute lymphoblastic leukemia in remission. Blood 54:468