ALLOGENEIC BONE MARROW TRANSPLANTATION AFTER FRACTIONATED TOTAL BODY IRRADIATION IN CHILDREN WITH ACUTE LEUKEMIA - OWN PRELIMINARY CLINICAL RESULTS.*

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INTRODUCTION

The results of conventional chemotherapy in children with acute leukemia have improved considerably over the last few years, leading to the cure rate of approximately 70% in children with acute lymphoblastic leukemia (ALL) (Nesbit and Woods, 1992; Reiter et al; Riveira et al, 1993) and 40% in those with acute myeloid leukemia (AML) (Dahl et al, 1990; Nesbit and Woods, 1992; Ritter et al 1992). However, especially in certain subgroups of children with negative prognostic factors, the results of chemotherapy remain still unsatisfactory (Grier et al, 1987; Riehm et al, 1992). In addition, children who relapse after conventional therapy for acute leukemia are seldom cured, particularly when the duration of the first complete remission (CR) is short (Bogusławska-Jaworska et al, 1994; Horowitz and Bortin,1993; Wieczorek et al, 1994). In children with poore prognostic factors at initial diagnosis or in those who have relapsed after standard chemotherapy allogeneic bone marrow transplantation (BMT) may be a therapeutic option provaiding sustained disease-free survival (Chessells et al, 1992; Dahl et al, 1990; Dopfer et al, 1991; Ebell et al, 1996;Niethammer et al, 1996). Conventional preparative regimen for BMT in patients with acute leukemias consists of total body irradiation (TBI) and cyclophosphamide (Thomas et al, 1977). However, numerous early and late complications have been attributed to TBI, especially in growing children (Dopfer and Niethammer, 1993; Petersen and Bearman, 1994). Besides, TBI can be carried out only in experienced and properly equiped radiation centers and is a time consuming and expensive procedure. All of these reasons gave rise to the search for alternative radiation-free conditioning regimens for BMT in children, that would be less toxic and easier available than TBI, but would have comparable myeloablative and antileukemic efficacy. One of the most promising such chemoconditioning regimens has been the one proposed by Tutschka et al. , which consisted of high dose busulfan and cyclophosphamide, and was then supplemented with etoposide (VP 16). At present, sufficient data for the evaluation of relapse rates following this regimen are available only for patients with AML and chronic myelocytic leukemia (CML) (Kolb et al, 1993). These studies, as well as the Polish experience in pediatric patients (Kaczmarek-Kanold, 1994) demonstrate that the busulfan-containing regimen is equivalent to TBI-containing regimens in AML and CML. According to Tutschka et al. (Tutschka et al, 1987) busulfan might have also an antilymphoblastic effect, and thus it might replace TBI also in ALL patients. However, in children with ALL in II CR prepared for BMT with busulfan we have observed high incidence of leukemia relapse after transplantation (Wachowiak et al, 1995), and therefore we concluded that despite some practical advantages at this point busulfan might not be able to replace TBI as conditioning regimen for BMT in ALL. In addition, it is nowadays controversial whether busulfan is really less toxic than TBI, because since TBI is carried out in fractionated manner (fractionated total body irradiation; FTBI) (Shank et al, 1983)

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the incidence of veno-occlusive disease (VOD) and hemorrhagic cystitis is even higher in recipients conditioned with busulfan than in those prepared with FTBI, and interstitial pneumonia incidence is similar in both groups of patients (Kolb et al, 1993). For mentioned above reasons in our institution since 1993 all children with ALL above 4 years of age as well as children with AML demonstrating high risk of VOD are prepared for BMT excusively with FTBI, and we report here our preliminary results of the treatment in these children.

PATIENTS AND METHODS

Eight children with acute leukemia (median age: 7 years, range 5-15) received BMT after FTBI (Table 1). Except one child transplanted from a syngeneic twin, all children have been transplanted from HLA-identical MLC non-reactive siblings. Diagnosis consisted of ALL in II CR (Dopfer et al, 1991), ALL in I CR (1) and AML in I CR (Barrett et al, 1989). Five of 6 patients in II CR of ALL had isolated bone marrow relapses, while one of them had combined marrow/testicular relapse. In all children except one there was an early relapse of ALL, i.e. < 18 months after diagnosis. The child with ALL in I CR demonstrated a translocationt (Grier et al, 1987; Shank et al, 1983) (Riehm et al, 1992), while in child with AML in I CR the M5 morphology of blasts (Grier et al, 1987) has been observed, and thereby these two children fulfiled criteria for BMT in I CR. One child with ALL (patient no. 6) and the child with AML (patient no. 8) demonstrated before BMT a liver injury caused by initial chemotherapy and infection with hepatitis C virus (HCV). In all children both first and second CR were achieved with the same initial and relapse BFM-therapy protocols (Riehm et al, 1992; Ritter and Creutzig, 1992).

All children were conditioned for BMT by means of hyperfractionated TBI (2 x 1,5 Gy on 4 consecutive days) with lung shielding (Malicki et al, 1995) followed by etoposide in a single dose of 60 mg/kg i.v. (in 6 children) or followed by cyclophosphamide given in adose of 60 mg/kg i.v. on each of two consecutive days (2 children with liver injury). In five children prophylaxis of acute graft-versus-host disease (aGvHD) consisted of cyclosporin A (CsA) and methotrexate (MTX), while in two children with liver injury (patients no. 6 and no. 8) CsA plus prednisolone have been given. The child transplanted with syngeneic marrow received no aGvHD prophylaxis.

Informed consent was obtained from the parents for the treatment. The date of analysis was April 5, 1996.

RESULTS

Marrow engraftment occured in all patients as shown by increasing peripheral blood cell counts. The median duration of neutropenia (absolute neutrophil count < 0,5 x 10^9/l) was 18 days (range 13-24). Median time to achieve a self-sustained platelet count > 30 x 10^9/l was 20 days (range 13-35). Hematopoietic status was normal in all survivors at the time of analysis.

There was no severe transplant-related complications. Only moderate aggravation of hepatic function was observed early post-BMT in two children (patients no. 6 and no. 8) transplanted despite liver injury caused by initial chemotherapy and HCV-infection. Acute GvHD grade I/II was observed only in one child and no chronic GvHD were documented.

The follow-up is shown in Table 1. Bone marrow relapses occured 3 and 5 months after BMT respectively in two children transplanted for ALL in II CR after early relapse. Six children remain in second CR ranging from 3 to 38 months (median: 11 months) after transplantation.

Patients characteristics, conditioning regimen and results of the treatment

Patient no.	Age (yrs)	Diagnosis	I CR Duration (month) & Site of Relapse	Conditioning Regimen	GvHD Prophylaxis	Acute GvHD	Chronic GvHD	Status (days)	Length of Follow-up /months
1.	11	ALL in II CR	72/BM	FTBI/VP	syngen	-	-	Alive	39
2.	15	ALL in II CR	6/BM	FTBI/VP	CsA/MTX	0	0	+ 92 relapse	
3.	8	ALL in II CR	10/BM/T	FTBI/VP	CsA/MTX	I/II	0	Alive	22
4.	5	ALL in II CR	16/BM	FTBI/VP	CsA/MTX	0	0	Alive	13
5.	10	ALL in II CR	8/BM	FTBI/VP	CsA/MTX	0	0	+ 139 relapse	
6.	8	ALL in II CR Liver injury HCV pos.	7/BM	FTBI/Cy	CsA/PRED	0	0	Alive	3
7.	6	ALL in I CR Ph (+)	7	FTBI/VP	CsA/MTX	0	0	Alive	9
8.	8	AML - M5 in I CR Liver injury HCV pos.	12	FTBI/Cy	CsA/PRED	0	0	Alive	7

Abbreviations: CR, complete remission; BM, bone marrow; T, testis; VP, etoposide; Cy, cyclophosphamide; FTBI, fractionated total body irradiation; GvHD, graft-versus-host disease; CsA, cyclosporin A; MTX, methotrexate; PRED, prednisone

DISCUSSION

The number of children with acute leukemia who have been transplanted in our institution with bone marrow after FTBI-containing conditioning regimen is up to now low and in addition the follow-up in these children is relatively short. For these reasons we can not draw any firm conclusion concerning our preliminary results. However, two relapses in 6 children with ALL conditioned for BMT with FTBI seem to be at this point somewhat better result in compare with 4 relapses that we have observed earlier in 6 children with ALL prepared for transplantation with busulfan-containing regimen (Wachowiak et al, 1995). The results of allogeneic BMT in acute leukemia depend on many factors, i.e. kind of leukemia, patient's age, phase of the leukemia (I, II or subsequent CR, partial remission), kind of relapse (localisation, duration of the I CR), type of initial and relapse treatment (Barrett et al, 1989; Dopfer et al, 1991). In our study, all children have been treated with initial and relapse BFM-therapy protocols. All children with ALL were in II CR, except one child in I CR. In addition, children transplanted in our institution were prepared for BMT in the similar manner as children with ALL reported from German/Austrian BMT Working Party (Dopfer et al, 1991; Niethammer et al, 1996). On account of all mentioned above similarities that concern factors influencing BMT outcome our results could be first of all refered to the results reported from this Working Party and from BFM-Group. According to the last reports of German/Austrian BMT Party (Niethammer et al, 1996) and BFM-Group (Ebell et al, 1996) an actuarial event free survival (pEFS) is respectively 65% and 69% for children with high risk ALL in I CR, and 56% for children with ALL transplanted in II CR after early bone marrow or combined relapse (Dopfer et al, 1991; Niethammer et al, 1996). For children with AML undergoing allogeneic BMT in I CR the actuarial pEFS was 62% (Niethammer et al, 1996). As many as 2 early relapses after BMT in 8 children transplanted for acute leukemia in our center along with low incidence of acute GvHD and no severe conditioning related toxicity may suggest, that efforts should be aimed at
reducing the relapse rate in these children by intensification of the conditioning regimen to receive better antileukemic effect and by reduction of the GvHD prophylaxis intensity to protect the graft-versus-leukemia effect (Horowitz et al, 1993). For example, it seems that in children with ALL who present standard risk of transplant-related toxicity the conditioning regimen could be safety intensified by addition to FTBI both VP-16 and cyclophosphamide as it was proposed by Spitzer et al. (Spitzer et al, 1989) for patients with high-risk hematologic malignancies. Besides, to improve the antileukemic effect of FTBI it could be

supplemented in boys according to Shank et al. with electron boost (4 Gy) to the testicles and in children with highest risk of leukemia relapse higher total dose of FTBI should be considered, for example of 14,4 Gy as proposed by Brochstein et al. The low incidence of acute GvHD and no chronic GvHD in our children suggests that the intensity of GvHD prophylaxis could be reduced, i.e. prophylaxis with CsA only without MTX might be sufficient to protect recipient of allogeneic bone marrow against GvHD and at the same time might favour better graft-versus-leukemia effect (Horowitz and Bortin, 1993).

Only moderate aggravation of liver function that has been seen in two children with pre-BMT severe liver injury seems to confirm observation that FTBI is less toxic for live than busulfan (Kolb et al, 1993) and that patients with liver malfunction FTBI rather than busulfan should be used.

According to our experience the conditioning regimen for allogeneic BMT with FTBI is well tolerated in children with acute leukemias, however, its antileukemic efficacy, especially in children with ALL, requests further improvement by optimazing the antileukemic potential of FTBI, chemotherapy and the graft-versus-leukemia effect.

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