Aim of the study: To report the long-term outcome in patients with leukaemias, who had conditioning regimens including total body irradiation (TBI) prior to bone marrow transplantation (BMT), and to establish independent factors correlated with treatment outcome.

Material and methods: Between January 2002 and December 2007, 18 patients, 11 males and 7 females with median age of 12 years (range 8-50), received TBI. Initial diagnoses were acute lymphoblastic leukaemia (ALL) 11 (61%), acute myeloid leukaemia (AML) 4 (22%), and chronic myeloid leukaemia (CML) 3 (17%). Pre-transplantation disease status was defined as remission 11 (61%), progression 4 (22%), and chronic phase 3 (17%). All the patients were conditioned with a high-dose chemoradiotherapy regimen including fractionated TBI delivering 10 to 12 Gy in 15 (73%) and a single fraction of 2 Gy in 3 (17%) of the cases. TBI was performed in alternate prone and supine positions with a 60 Co machine. In 13 (72%) patients transplantation was carried out from an HLA-identical related donor and in 5 (28%) from an unrelated donor. Seventeen allogeneic transplantations were of peripheral blood stem cells and 1 was of bone marrow stem cells. Post-transplantation clinical, biological, and functional evaluations were performed on days 30, 100, 180, at 1 year, and annually thereafter. Each evaluation included an assessment of the study end points: marrow chimerism, disease status (complete remission or relapse), survival status (alive or dead), treatment-related toxicity (TRT), treatment-related mortality (TRM) and graft-versus-host-disease (GvHD).

Results: Median follow-up from BMT was 27 months (range 3-52). Sixteen patients achieved engraftment, 2 patients had primary graft failure. Seven of 18 (39%) evaluable patients developed acute GvHD, 6 (35%) patients developed chronic GvHD. At the time of reporting 9 of 18 patients remain alive and in remission. Nine patients died, 4 (22%) because of relapse and 5 (28%) because of TRM. The cause of TRM was acute GvHD (2) and fatal – hepatic toxicity (1), neurological toxicity (1) and idiopathic pneumonia syndrome (1). The Kaplan-Meier estimates of 1- and 3-year overall survival (OS) for patients were 58%:31%, respectively. In univariate analysis, no differences were observed regarding age, gender, initial diagnosis, status of the disease, total dose of TBI, HLA-identity, and effect of acute GvHD. Chronic GvHD was associated with increased OS (p = 0.05).

Total body irradiation and allogeneic bone marrow transplantation – Sofia University Hospital experience

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During the past 40 years, haematopoietic stem cell transplantation (HSCT) has become accepted as routine treatment for many patients with neoplastic and hereditary diseases. It is furthermore acknowledged as the basic therapy for high-risk patients with life-threatening haematological diseases rather than the last therapeutic chance. The number of patients receiving transplants has increased exponentially to currently about 25,000 per year [1]. The past decades of HSCT have been marked by gradually improving results. However, despite the considerable progress, many problems remain and now the cure rate for relapsed acute leukaemia is not appreciably higher than before.

Total body irradiation (TBI) is an important component of bone marrow transplantation (BMT). TBI-conditioning regimens have produced better transplant outcome compared to that after chemotherapy-only regimens [2, 3]. During the last decades high-dose chemoradiotherapy including TBI has been considered to have a recognized therapeutic potential in acute high-risk lymphoblastic (ALL) and myeloid leukaemias (AML), in chronic myeloid leukaemia (CML) and in more than 20 other indications, including lympho- and myeloproliferative diseases and solid tumours.

It is just during the last decade that the Bulgarian oncological community has gained a deeper insight and knowledge in the field of HSCT. The first autologous HSCT was carried out in Bulgaria in 1997, the first TBI with allogeneic HSCT in 2002, and the first allogeneic HSCT with non-myeloablative conditioning regimen including TBI of 2 Gy in 2005.

Presenting the first Bulgarian clinical experience, we report the long-term outcome in 18 patients with leukaemias treated at the Medical University of Sofia with conditioning regimens including TBI before allogeneic HSCT and the established independent factors correlated with the treatment outcome.

Material and methods

Patient characteristics

From January 2002 to December 2007, 18 patients received TBI as the conditioning regimen for allogeneic HSCT at the Radiotherapy and Haematology Department of the Medical University of Sofia. There were 11 (69%) males and 7 (31%) females, with a median age of 12 (range 8-50) at the time of BMT. The ages of 8 and 12 years are most often encountered – 3 patients for each. The initial diagnoses were ALL 11 (61%), AML 4 (22%), and CML 3 (17%). Pre-transplantation disease status was defined as remission 11 (61%), progression 4 (22%) and chronic phase 3 (17%).

Large field treatment stationary technique, based on the Cobalt-60 teletherapy unit, and a specially designed patient table, movable above and below the floor level, were used. Field sizes of up to 80 × 80 cm^2 at an SSD of 300 cm were achieved. The requirement for dose rate of 5-10 sGy/min was adhered to. Personalized lung shields were used to compensate different density and to reduce the lung dose to 8 Gy. The received radiation doses to various parts of the body were monitored by in vivo dosimetry using

Conclusion: The achieved 3-year OS and TRM are comparable to those cited in the reference literature. The development of chronic GvHD exerted a significant impact on the estimated OS. However, the small number of cases precludes a definitive conclusion on the efficacy of the regimens used and further evaluation is required.

Key words: haematopoietic stem cell transplantation, total body irradiation.

semiconductor detectors placed anteriorly and posteriorly on a number of specified body sites.

Treatment consisted of a high-dose chemoradiotherapy conditioning regimen including a single fraction of 2 Gy or a fractionated TBI with a dose of 10-12 Gy.

Post-transplantation clinical, biological, and functional evaluations were performed on days 30, 100, 180, at 1 year, and annually thereafter. Each evaluation included an assessment of the study endpoints: marrow chimerism, disease status (complete remission or relapse), survival status (alive or dead), treatment-related toxicity (TRT), treatment-related mortality (TRM) and graft-versus-host-disease (GvHD).

Endpoints and statistical analysis

Overall survival (OS) was assessed using the Kaplan-Meier method and was determined from the day of transplantation (day 0). Kaplan-Meier survival curves were constructed to assess the probability of survival during the follow-up period, and a log-rank test was used to compare survival curves. A p value of less than 0.05 was considered to indicate statistical significance in the comparisons between groups. Factors considered potentially relevant for OS were as follows: age at BMT (more or less than 20 years of age), gender, diagnosis, status at BMT, total TBI dose received, HLA identity, and the occurrence of acute or chronic GvHD. Data analysis was performed using SPSS Version 13.1.

Results

Patient characteristics are detailed in Table 1. Median follow-up from BMT was 27 months (range 3-52).

TBI was performed through two (9) or three (9) pairs of parallel opposed fields in the prone/supine position. The median dose rate varied between 5.1 and 12.3 cGy/min mainly due to source decay and replacement during the 6-year period of application. In 15 patients lung shielding was used and the lung dose was limited to 8 Gy. The doses applied using the TBI technique were uniform and most parts of the body received within +6.9% and –1.7% of the dose delivered to the prescription point.

Treatment consisted of a fractionated TBI delivering 10 to 12 Gy in 15 (83%) of the patients, and a single fraction of 2 Gy in 3 (17%). Two patients (11%) received TBI of 10 Gy (5 fractions in 5 days), 5 (27.8%) received TBI of 10 Gy (6 fractions in 3 days), and 8 (44.4%) received TBI of 12 Gy (6 fractions in 3 days).

The conditioning regimen was cyclophosphamide, Vepesid and TBI (10) (55.5%), cyclophosphamide and TBI (3) (16.6%), melphalan, fludarabine, ATG and TBI (2) (11.1%), and a non-myeloablative conditioning regimen including fludarabine and TBI of 2 Gy (3) (16.6%).

All patients received their regimen for a first HSCT. In 13 (72%) patients transplantation was performed from a HLA-identical related donor and in 5 (28%) from a donor genotypically disparate from their recipients, partially compatible. In the majority of patients (72%) brothers and sisters were donors. From the 18 allogeneic transplantations 17 were peripheral haemopoietic blood stem cells and 1 was bone marrow stem cells. In 8 patients a single-time mobilisation and collection of peripheral stem cells was performed from both the donor and the patients for a reserve cellular pool, and a repeated (2-times) mobilisation was applied in 10 patients. There was T-cell depletion of the graft of 3 donors to prevent GvHD in case of haploidentity between donor and recipient. The median (range) number of CD34+ cells/kg was 4.16 (0.59-10) $\times$ 10^6, infused while fresh into the recipient within 24 hours of collection. The date of marrow infusion was defined as transplantation day 0 and +1.

Sixteen patients achieved engraftment, 2 patients had primary graft failure. No mixed chimerism or secondary graft failure was encountered in the

remaining patients. Seven of 18 (39%) evaluable patients developed acute GvHD, 6 (35%) patients developed chronic GvHD.

At the time of reporting 9 of 18 patients remain alive and in remission. Nine patients died, 4 (22%) because of relapse and 5 (28%) because of TRM. The most common cause of TRM was acute GvHD (2), and fatal outcomes were observed due to hepatic toxicity in the form of hepatitis C activation (one patient), neurological toxicity in the form of a haemorrhage of the brain (one patient) and idiopathic pneumonia syndrome (one patient).

Two relapses developed – in one of the patients a systemic relapse of the disease occurred and in the second patient after two meningitis relapses, a systemic relapse followed without subsequent remission.

With a median follow-up of 27 (range 3-52) months, the Kaplan-Meier estimates of OS for patients are shown in Figure 1. The estimated 1-, 2-, and 3-year OS in 18 patients with leukaemias are 58% : 58% : 31%, respectively.

From the *patient-related characteristics* the *age* of the patients (≤ 20 yrs of age; > 20 yrs of age) did not turn out to be a significant prognostic factor ($p = 0.15$), regardless of the better OS of patients > 20 yrs of age compared to those ≤ 20 yrs of age (80% : 19% 3-year OS). According to *gender* there was a trend for better survival in males compared with females, with the ratio of 3-year OS 58% : 14%, respectively, which was also statistically insignificant ($p = 0.20$).

From the *disease-related characteristics*, according to the *type of leukaemia* the patients with ALL and AML exhibited 1-, 2-, and 3-year OS of 48% : 48% : 32% vs. 50% : 50% : 50%, respectively, $p = 0.95$. From the 3 patients with CML in the chronic phase, one patient died as a result of TRM within the 3rd month after transplantation and the other two died within the 27th month. The survival rate versus the *disease status* at the stage of transplantation, respectively the state of remission, progression or chronic phase, is presented in Figure 2. The achieved 1- and 3-year OS rate in patients with the status of remission is 70% : 70%. Three patients, in whom transplantation was performed in the status of progression, died by the 14th month. The three patients in the state of chronic phase of CML, which is assumed to be the most suitable for implementing BMT, died by the 27th month. However, no statistically significant difference was established between the three groups, probably due to the small number of observed cases ($p = 0.11$).

From the *treatment-related characteristics* the performed *TBI* with 12 Gy/6 fractions/3 days exhibits better, although insignificant ($p = 0.26$) 1-and 2-year OS compared to the implemented TBI with 10 Gy/6 fractions/3 days, 86% : 68% vs. 60% : 40%, respectively. Regardless of the observed better 1-year OS for the patients with complete *compatibility* between donor and recipient compared with those with incomplete compatibility, 75% vs. 40%, respectively, the differences are also insignificant, $p = 0.36$. The patients who did not develop *acute GvHD* (11 patients) exhibit better 1- and 2-year OS compared to those who developed the reaction (7 patients), 80% : 60% vs. 43% : 43%, respectively, statistically insignificant, $p = 0.29$. The established statistically significant difference ($p = 0.02$) in OS of the patients depending on the development of *chronic GvHD* (Fig. 3) is of special interest. One-, 2-, and 3-year OS in patients with and without chronic GvHD are 83% : 83% : 83% vs. 45% : 34% : 11%, $p = 0.02$ respectively.

The results of the univariate analysis of some patient-, disease-, and treatment-related characteristics are presented in Table 2. In Cox regression analysis OS rates were statistically positively affected by the presence of chronic GvHD vs. its absence ($p = 0.05$) (Table 3).

Table 1. Demographic, clinical and treatment characteristics of patients with haematological diseases

Characteristic	Number	(%)
Patients	**18**	**100**
Gender		
male	11	61
female	7	39
Age		
mean	20	
range	8 -50	
Diagnosis		
ALL	11	61
AML	4	22
CML	3	17
Disease status		
remission	11	61
progression	4	22
chronic phase	3	17
TBI dose (Gy)		
2	3	
10	7	
12	8	
TBI fractionation		
1 day	3	
3 days	13	
5 days	2	

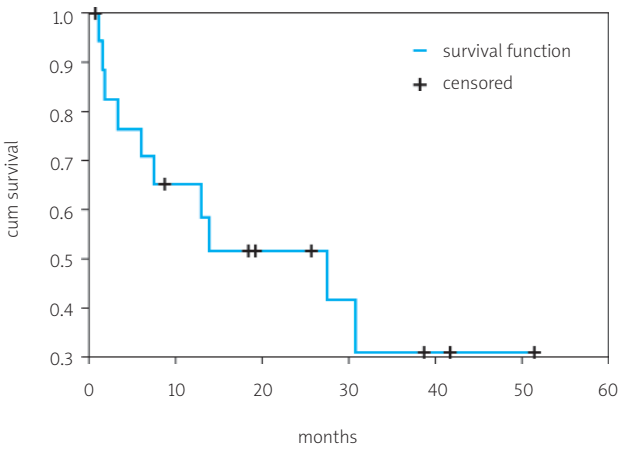

Fig. 1. Cumulative overall survival in 18 patients with TBI and allogeneic BMT

Discussion

Leukaemias are aggressive diseases and require intensive cytoreduction in the immediate pre-transplant period. At the present stage of knowledge in the field of HSCT no

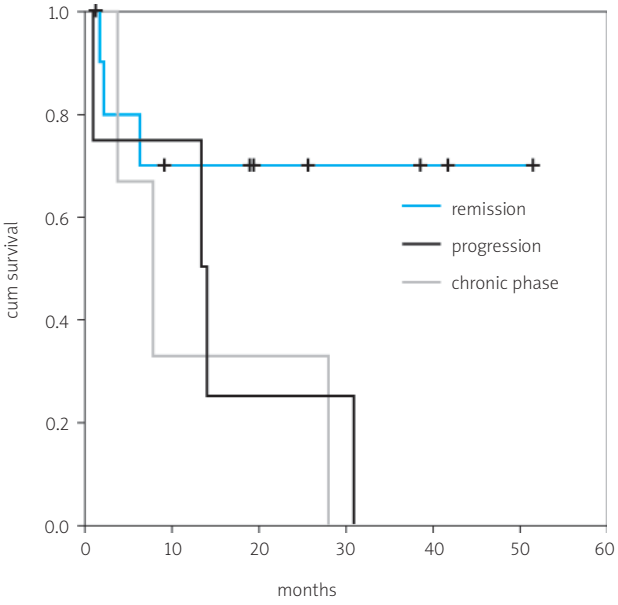

Fig. 2. Overall survival depending on disease status

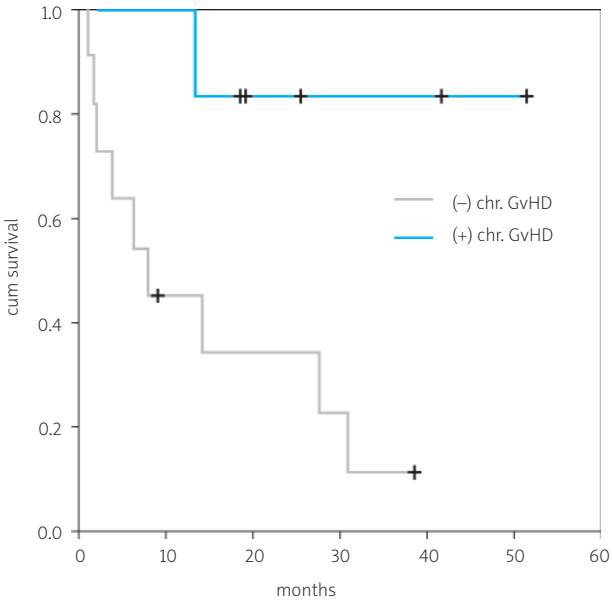

Fig. 3. Overall survival depending on chronic GvHD

Table 2. Results of the univariate analysis of patient-, disease- and treatment-related characteristics

Characteristic	Cumulative OS (months)	St. error	95% CI	*p* value
Gender				
Male	27.3	5.18	16.56-38.08	0.20
Female	18.6	6.64	5.58-31.60	
Type of leukaemia				
ALL	21.6	5.38	11.06-32.15	0.95
AML	29.3	11.23	7.33-5.37	
CML	19.6	9.26	1.46-37.77	
Status of disease				
Remission	36.9	7.01	23.21-50.68	0.11
Progression	14.8	6.13	2.80-26.82	
Chronic phase	13.0	7.42	0-27.54	
Type of conditioning regimen				
Myeloablative	24.17	5.46	13.47-34.88	0.72
Non-myeloablative	17.51	6.58	4.62-30.40	
TBI, Gy				
3 (2 × 2 Gy)	28.61	5.94	16.96-40.26	0.26
3 (2 × 1.67 Gy)	20.71	7.77	5.47-35.4	
HLA identity				
Complete	27.53	5.83	16.11-38.95	0.36
Incomplete	12.11	4.97	2.38-21.85	
Acute GvHD				
(+) acute GvHD	17.50	6.38	5.00-30.00	0.29
(–) acute GvHD	29.62	6.71	16.47-42.77	
Chronic GvHD				
(+) chron. GvHD	45.05	5.83	33.63-56.47	0.02
(–) chron. GvHD	14.63	4.19	0.42-22.83	

Table 3. Cox regression analysis

Characteristic	B	SE	Wald	df	OR	95% CI	*p* value
Chronic GvHD	–2.063	1.059	3.793	1	0.127	0.016-1.013	0.05

explicit data exist about the advantages of a definite myeloablative conditioning regimen, making it superior to the other ones. ALL registry analysis suggests that TBI-based regimens are superior [4]. Concerning CML, no differences were established between the various myeloablative regimens, but the BU/CY regimen yielded worse therapeutic results compared to TBI/CY in AML [4, 5]. At the present stage it is assumed that TBI has better therapeutic possibilities in patients with more advanced disease [6].

The lack of benefit of conditioning regimen dose intensification and the recognition of the contribution of graft-versus-tumour activity to disease eradication prompted the development of low-dose regimens. Studies indicate that these non-myeloablative regimens can facilitate full donor engraftment while sparing the patient many of the toxicities related to traditional high-dose therapy, allowing transplantation to be performed in older patients and in patients with comorbid conditions with contraindications to high-dose therapy, as was the case with our first three patients [7, 8]. In our first prospective study on TBI with subsequent allogeneic BMT, we implemented the basic myelo- and non-myeloablative conditioning regimens finding application in international oncological practice.

Relapse development is one of the basic reasons for failure of treatment, carried out even at the early stage of the disease [9–11]. According to Craddock *et al*. it varies from 30% to 40% in patients transplanted after the 1st or 2nd remission [12]. The relapse probability after transplantation at a more advanced stage of the disease is from 20% to 70% [13]. The relapse rate of 11% in our study does not differ substantially from that cited in the literature [3].

The TRM value of 28% established by us is comparable to other series with patients of similar disease status [14, 15]. The results obtained by us point out once again that one of the major problems in this group of patients is not only the tolerance towards the marrow engraftment but also the treatment-related toxicity and mortality during the first years after transplantation.

Despite the limited material, including 18 patients, transplanted within 6 years, the first achieved therapeutic results are of special interest for us. When evaluating them, it has to be taken into account that our study on the therapeutic potential of TBI and allogeneic BMT was started for patients with terminal leukaemia with fully exhausted therapeutic possibilities – i.e., as an attempt to carry out "salvage therapy". It was only later that the recommendable international criteria for including the patients in the clinical protocol started to be adhered to. The recorded 31% 3-year OS (respectively 48% : 32% 2-, and 3-year OS for the most numerous group, 11 patients with ALL) is close to the one cited in the literature [9, 10]. Our first clinical observations have demonstrated the efficacy of non-myeloablative strategies as well. From the 3 patients for whom the non-myeloablative regimen has been applied, one patient died as a result of TRM, while the other two patients are alive without evidence of recurrence within 18 and 24 months after the performed transplantation.

Recipient factors are important in predicting transplant outcomes. The age of the patients is one of the most often discussed issues. The maximum age of transplant candidates has increased in the course of time. Over the last 5 years the proportion of patients receiving allografts above the age of 50 years has approached 15%. It is considered that with the exception of newborns, for the rest of patients TRM increases with age [16]. According to Craddock *et al*. TRM is 19% for patients with AML ≤ 20 years of age and 39% for those > 35 years of age [12]. Our data do not coincide with the better results and lower TRM cited in the literature for younger individuals. We could explain a similar result both with the small and heterogeneous clinical material and with the inclusion in the beginning of the study of children with terminal leukaemia. The considerably better OS in men turned out to be also statistically insignificant ($p = 0.02$).

Among the most important recipient factors is disease status at transplant. During the last decade about 60% of BMT in high risk ALL, AML and chronic CML are carried out in 1st remission or the chronic phase of the disease. Only 15% of the transplanted patients are in the advanced stage of disease [17]. In our study 22% of the patients are in the state of relapse, and 78% are in the state of remission or chronic phase of the disease. Survival after HSCT is 48-49% for patients with ALL in 1st remission, 29-34% for patients in 2nd remission and 15-18% for patients with advanced disease [9, 10]. Disease-free survival (DFS) for patients with CML in the 1st chronic phase, accelerated phase or blast phase of the disease after BMT is 40% to 60%, 26% to 38%, and less than 15%, respectively [18]. The same is valid also for AML. As with relapse rates, patients with more advanced disease have significantly higher mortality rates, in large part due to progressive disease. The impact of disease status has been verified, although with statistical insignificance, by our first study too.

At present, no consensus has been reached as to which TBI regimen is the most effective in reducing the target leukaemia cells and decreasing the incidence of acute and late effects of treatment. In many of the studies it is difficult to separate the effects of fractionation from those of total dose, as both changed in the regimen used. Dosage ranging from 5.5 Gy as a single exposure to 15.75 Gy in multiple daily fractions has been used [19-21]. In general, higher TBI doses are used for advanced leukaemia or HLA-disparate grafts. There is some evidence that higher total doses of TBI may be more effective at preventing relapse, but these benefits have been offset by increasing non-relapse mortality in the first 6 months after treatment, so that the OS of the patient population was not improved [19, 22, 23]. In a study from Italy data are reported for 55% relapse frequency at the 7th year in patients with AML and CML, subjected to allogeneic BMT and TBI with a dose < 9.9 Gy, and only 11% for a dose > 9.9 Gy ($p = 0.0005$) [24]. This difference ultimately had a major impact on survival rate: 74% OS at the 8th year for the group with a dose > 9.9 Gy and only 38% for a dose < 9.9 Gy ($p = 0.005$). Additional data analysis reveals that total dose was the most significant factor affecting survival [25]. Most contemporary regimens deliver a total dose of 10 to 15 Gy using a variety of fractionation [2, 26, 27]. In our study regardless of the better results with a TBI dose of 12 Gy vs. 10 Gy, no significant difference has been found for the achieved survival rate, $p = 0.26$.

The median incidence of acute GvHD is about 40% (but ranges from 10 to 80% according to the number of risk factors) and of chronic GvHD is 20% to 50% of long-term

survivors, which correspond to the frequencies established by us, of 39% and 35%, respectively [1]. The experience accumulated so far proves the positive effect of chronic GvHD on relapse development frequency and in the more advanced stages of disease both reactions – the acute and the chronic ones – exert a positive impact on RFS[28]. The achieved 3-year OS for the patients from our study "with developed" and "without developed" chronic GvHD is in the proportion 83% : 11%, $p = 0.02$, which corresponds to the data cited in the reference literature.

On the basis of the comprehensive analysis of reference literature and on our modest experience we consider that the interpretation of the therapeutic results after BMT performance is difficult and often inadequate. However, we consider that with the enhancement of all steps of HSCT, from patient selection and conditioning regimen selection to prevention of GvHD, the results of HSCT have continued to improve.

In conclusion, the first prospective study of TBI and allogeneic HSCT in Bulgarian oncoradiological practice is in progress. The achieved 3-year OS rates and the observed TRT and TRM are comparable to the average ones cited in the reference literature. The development of chronic GvHD exerts a significant impact on the achieved survival rate.

However, the small number of cases precludes a definitive conclusion on the efficacy of the regimens used and further evaluation is required.

References

1. Haematopoietic Stem Cell Transplantation. The EBMT Handbook. Apperley J, Carreras E, Gluckman E, Gratwohl A, Masszi T (eds.). 5th ed. 2008.
2. Davies SM, Ramsay NK, Klein JP, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol 2000; 18: 340-7.
3. Woolfrey AE, Anasseti C, Storer B, et al. Factors associated with outcome after unrelated marrow transplantation for treatment of acute lymphoblastic leukemia in children. Blood 2002; 99: 2002-8.
4. Blaise D, Maraninchi D, Archimbaud E, et al. Allogeneic bone marrow transplantation for acute myeloid leukemia in first remission: A randomized trial of a busulfan-cytoxan versus cytoxan – total body irradiation as preparative regimen: A Report from the Group d'Etudes de la Greffe de Moelli Osseuse. Blood 1992; 79: 2144-50.
5. Sullivan K, Siadak M. Long term follow-up after hematopoietic stem cell transplantation. In: Cancer patient follow-up. Johnson Fl, Virgo KS (eds). Mosby, St. Louis, Missouri 1998; 490-518.
6. Socié G, Clift RA, Blaise D, et al. Busulfan plus cyclophosphamide compared with total-body irradiation plus cyclophosphamide before marrow transplantation for myeloid leukemia: long-term follow up of 4 randomized studies. Blood 2001; 98: 3569-74.
7. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood 1997; 89: 4331-6.
8. Khouri IF, Saliba RM, Giralt SA, et al. Nonablative allogeneic hematopoietic transplantation as adoptive immunotherapy for indolent lymphoma: low incidence of toxicity, acute graft-versus-host disease, and treatment-related mortality. Blood 2001; 98: 3505-99.
9. Chaidos A, Kanfer E, Apperley J. Risk assessment in haemotopoietic stem cell transplantation: disease and disease stage. Best Pract Res Clin Haematol 2007; 20: 125-54.
10. Loberiaza F. Summary slides 2003 – part III. IMBTR/ABMTR Newsletter 2006; 10: 6-9.
11. Rizzo J. 1998 IBMTR/HBMTR summary slides on state-of the-art in Blood and Marrow Transplantation. HBMTR Milwankee WI USA, IBMTR/ABMT Statistical Center, Medical Collage of Wisconsin, Newsletter 1998; 5: 4-10.
12. Craddock CF, Labopin M, Finke J, et al. Factors Determining Survival after Unrelated Donor Stem Cell Transplantation in Primary Refractory Acute Myeloid Leukemia. Blood 2008; 112: 211-2.
13. Gale R, Butturini A, Bortin M. What does total body irradiation do in bone marrow transplants for leukemia? Int J Radiat Oncol Biol Phys 1991; 20: 629-32.
14. Barker JN, Davies SM, DeFor T, et al. Survival after transplantation of unrelated donor umbilical cord blood is comparable to that of human leucocyte antigen-matched unrelated donor bone marrow: results of a matched-pair analysis. Blood 2001; 97: 2957-71.
15. Guckman E, Rocha V, Arcese W, et al. Factors associated with outcomes of unrelated cord blood transplant: guidelines for donor choice. Experimental Hematol, 2004; 32: 397-407.
16. Lee S, Klein J, Haagenson M, et al. Single or multiple HLA-A,B,C or DRB1 mismatches limits success of unrelated donor bone marrow transplantation. Blood, (ASH Annual Meeting Abstracts) 2006; 108: 55a (abstract 172).
17. Statistical Center of the International Bone Marrow Transplant Registry and Autologous Blood and Marrow Transplant Registry. Unpublished data 1995.
18. Couban S, Simpson D, Barnett M, et al. A randomized multicenter comparison of bone marrow and peripheral blood in recipients of matched sibling allogeneic transplants for myeloid malignancies. Blood 2002; 10: 1525-31.
19. Clift RA, Buckner CD, Appelbaum FR, et al. Long-term follow-up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. Blood 1998; 92: 1455-6.
20. Clift RA, Buckner CD, Appelbaum FR, et al. Allogeneic marrow transplantation in patients with acute myeloid leukemia in first remission: a randomized trial of two irradiation regimens. Blood 1990; 76: 1867-71.
21. Blum W, Brown R, Lin H-S, et al. Low-dose (550 cGy), single-exposure total body irradiation and cyclophosphamide: consistent, durable engraftment of related-donor peripheral blood stem cells with low treatment-related mortality and fatal organ toxicity. Biol Blood Marrow Transplant 2002; 8: 608-18.
22. Gopal R, Ha CS, Tucker SL, et al. Comparison of two total body irradiation fractionation regimens with respect to acute and late pulmonary toxicity. Cancer 2001; 92: 1949-58.
23. Cohen D. Idiopathic pneumonia syndrome after bone marrow transplantation: the role of pre-transplant radiation conditioning and local cytokine dysregulation in promoting lung inflammation and fibrosis. Int J Exp Pathol 2001; 82: 101-13.
24. Frassoni F, Scarpati D, Bacigalupo A, et al. The effect of total body irradiation dose and chronic graft versus host disease of leukemic relapse after allogeneic bone marrow transplantation. Br Haematol 1989; 73: 211-216.
25. Scarpati D, Frassoni F, Vitale V, Corvo R, Franzone P, Barra S, Guenzi M, Orsatti M. Total body irradiation in acute myeloid leukemia and chronic myelogeneous leukemia: influence of dose and dose-rate on leukemia relapse. Int J Radiat Oncol Biol Phys 1989; 17: 547-52.
26. Vriesendorp HM, Chu H, Orchan TG, et al. Radiobiology of total body irradiation. Bone Marrow Transplant 1994; 14 (suppl 4): 4-8.
27. Socié G, Devegie A, Girinsky T, et al. Influence of the fractionation of total body irradiation on complications and relapse rate for chronic myelogenous leukemia. The groupe d'etude des greffes de moelle osseuse (gegmo). Int J Radiat Oncol Biol Phys 1991; 20: 397-404.
28. Sullivan K, Mori M, Sanders J, et al. Late complications of allogeneic and autologous marrow transplantation. Bone Marrow Transplant 1992; 10: 127-34.

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