ALLOGENEIC BONE MARROW TRANSPLANTATION IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKAEMIA IN THE FIRST AND SECOND COMPLETE REMISSION CONDITIONED WITH FRACTIONATED TOTAL BODY IRRADIATION AND CYCLOPHOSPHAMIDE OR ETOPOSIDE*

Jacek Wachowiak[1], Julian Malicki[2], Dariusz Buczkowski[1], Grażyna Stryczyńska[2], Grażyna Kosicka[2], Michał Leda[1], Anna Pieczonka[1]

[1]Department of Paediatric Haematology, Oncology and Haematopoietic Stem Cell Transplantation, The Institute of Paediatrics, ul. Szpitalna 27/33, 60-572 Poznań, Poland
[2]The Great Poland Cancer Centre, Poznań, Poland

Received February 14th, 2001; received in a revised form July 10th, 2002; accepted August 14th, 2002

ABSTRACT

Patients and methods: From 1993 to 2001 thirty-two children underwent bone marrow transplantation (BMT) for acute lymphoblastic leukaemia (ALL) (12 in I complete remission /I CR/ of high-risk /HR/ ALL, and 20 in II CR after early bone marrow or combined bone marrow/organ relapse). Except for two syngeneic all others were matched sibling donor transplants. All patients (pts) were conditioned with fractionated total body irradiation (FTBI) at a total dose of 12,6 Gy, given in 8 fractions during 4 days with lung shielding (9,4 Gy) and cyclophosphamide (CY) 60 mg/kg *i.v* for 2 days (total dose 120 mg/kg) (n = 1 in I CR and n = 11 in II CR) or etoposide (VP) 60 mg/kg *i.v* (n = 11 in I CR and n = 9 in II CR). Patients in I CR were given 1,1–4,9x10^8 nucleated cells /kg (med. 2,7x10^8/kg), while pts in II CR 1,9–4,0x10^8 nucleated cells/kg (med. 2,7x10^8/kg). For graft versus host disease (GvHD) prevention cyclosporin A (CsA) 3 mg/kg/d *i.v* was administered alone in 22 pts (n = 9 in I CR and n = 13 in II CR) or in combination with "short" methotrexate +/- prednisone in 8 pts (n = 3 in I CR and n = 5 in II CR). Two pts transplanted with syngeneic BM received no GvHD prevention. The regimen related toxicity (RRT) was graded according to the system developed by Bearman *et al*. (1988).

Results: Only mild or moderate expression of RRT was observed (GI toxicity I^0 - 80%, II^0 - 4%; stomatitis I^0 - 40%, II^0 - 20%; hepatic toxicity I^0 - 28%; renal, bladder and cardiac toxicity I^0 - 4%) and no transplant related deaths occurred (TRM = 0%). Among 12 pts transplanted in I CR only one child relapsed 4 months from BMT, while the remaining 11 pts are alive in continuous complete remission (CCR) with a median follow-up of 33 months (range 6 to 66 months) and 92% probability of a 5-year event free survival (pEFS). Of 20 children transplanted in II CR 6 relapsed 1-14 months from BMT (median 6,5 months). Thirteen of them remain in CCR with a median follow-up of 19.5 months (range 1 to 96 months) and with 66% probability of a 8-year EFS.

Conclusions: 1. In children with ALL the FTBI-12,6 Gy-containing regimen is well tolerated without life-threatening toxic complications. 2. The FTBI-12,6 Gy-containing regimen demonstrates very good antileukaemic efficacy for HR-ALL in I CR, but only limited efficacy for ALL in II CR. 3. In the context of good tolerance of FTBI in a total dose of 12,6 Gy and its limited antileukaemic efficacy in children with ALL in II CR the escalation of FTBI total dose from 12,6 Gy to at least 13,2 Gy appears to be justified in those children.

Key words: acute lymphoblastic leukaemia, fractionated total body irradiation, allogeneic bone marrow transplantation.

INTRODUCTION

Acute lymphoblastic leukaemia (ALL) remains the most frequent malignancy in children, comprising 30% of all childhood neoplasms [1]. Thanks to present-day chemotherapy about 85% children with ALL from a standard-risk group and 70% from a high-risk group have a chance to be cured [2, 3, 4]. On the contrary,

Material presented at Conference "Advances in Radiation Oncology: Diagnosis-Treatment Planning-Clinical Outcome", Poznań, April 19th – 21st, 2001.
*Supported by grant KBN 4 POSE 108 18.

in the case of relapsed ALL – especially in the case of a very early or early bone marrow relapse - the probability of sustained remission is significantly lower compared with primary ALL [5,6]. Therefore, in the majority of children in II CR of ALL, and also in those 8-10% who demonstrate very high-risk of relapse in I CR, bone marrow transplantation (BMT) is performed as a consolidation of conventional chemotherapy to improve the results of the treatment. For these reasons, ALL is the most frequent (53,4%) indication for BMT in childhood [7,8]. However, it is not yet established which preparative regimen for BMT assures in children with ALL the best results, i.e. the minimal regimen related toxicity along with maximal anti-leukaemic efficacy. According to our preliminary observations, the busulfan-based conditioning regimen – despite suggestions by other authors [9] - provided worse results than the total body irradiation (TBI)-containing regimen in children transplanted for ALL in II CR [10]. Therefore, since January 1993 all children over 2 years of age suffering from ALL and demonstrating indications for BMT have been conditioned for transplantation by fractionated TBI (FTBI) at a total dose of 12,6 Gy with lung shielding (9,4 Gy), supplemented with cyclophosphamide or etoposide.

PATIENTS AND METHODS

Patients

From 1993 to 2001, thirty-two children (12 females and 20 males) aged from 4 to 18 (median 10,5 years) underwent BMT for ALL.

Twelve patients, who demonstrated a very high risk (VHR) of leukaemia relapse (i.e. t(9; 22) or t(4; 11), and/or poor prednisone response, and/or no CR on day 33 of induction treatment according to the New York Protocol [11]), were transplanted in I CR. Transplantation was performed at least 3 months from the diagnosis (range 3-11 months; median 6 months).

Twenty patients obtained transplant in II CR after a very early (n = 2), early (n = 9) or late (n = 9) bone marrow (n = 18) or combined bone marrow/organ (n = 2) relapse. The Relapse was treated according to the ALL-REZ-BFM Protocols [6,12]. Children in II CR underwent transplantation 1 to 12 months from the relapse (median 5 months).

Patient/donor HLA typing

Except for two transplants from syngeneic twins, all other children were transplanted with allogeneic bone marrow from genotypically HLA-identical siblings.

Preparative regimen

All patients were conditioned for BMT by FTBI of a total dose of 12,6 Gy given in 8 fractions during 4 consecutive days (2 fractions/day) with reduction to 9,4 Gy in the lungs. Fifteen patients were irradiated with a Cobalt-60 unit, while 17 with a linear accelerator Mevatron with 15 MeV photons. A dose of 8.2 Gy was delivered from six lateral fields, and a dose of 4.4 Gy from four anterior-posterior fields. For Cobalt-60, the lateral fields were set at a source to the skin distance (SSD) of 275 cm with the dose rate in the midline of $6,67 \div 9,01 \bullet 10^{-2}$ Gy/min, and AP/PA fields were set at 183 cm with $17.75 \div 27,90 \bullet 10^{-2}$ Gy/min, respectively [13,14]. For the linear accelerator, the lateral fields were set at the SSD of 307 cm with the dose rate of $4,25 \bullet 10^{-2}$ Gy/min, and AP/PA fields at 206 cm with $10,65 \bullet 10^{-2}$ Gy/min, respectively. The method of FTBI has been descrybed in detail elsewhere [15].

In 12 children (1 in I CR and 11 in II CR) FTBI was followed by cyclophosphamide (CY) 60 mg/kg/day *i.v* for 2 days (total dose 120 mg/kg), while in the remaining 20 patients (11 in I CR and 9 in II CR) FTBI was supplemented with etoposide (VP-16) 60 mg/kg *i.v*.

Source and number of transplanted cells

All children were transplanted with bone marrow. Patients in I CR were given $1,1\text{-}4,9 \times 10^8$ NC/kg (med. $2,7 \times 10^8$/kg), whereas those in II CR obtained $1,9\text{–}4,0 \times 10^8$ NC/kg (med. $2,7 \times 10^8$/kg).

Graft-versus-host disease prophylaxis and grading

For graft versus host disease (GvHD), prevention cyclosporin A (CsA) was admi-

nistered alone in 22 patients (9 in I CR and 13 in II CR) or in combination with "short" methotrexate (MTX) +/- prednisone (PRED) in 8 pts (3 in I CR and 5 in II CR). CsA administration started 36 hours before transplantation and was continued intravenously until the patient could tolerate the oral form of the drug. The CsA level was monitored three, times weekly and the dosage was adjusted to maintain the whole blood level of 100 +/- 25 ng/ml until day +120 and then slowly tapered until day +150. Two patients transplanted with syngeneic bone marrow received no GvHD prevention.

Acute and chronic GvHD was graded according to standard criteria [16,17].

Regimen-related toxicity grading

Regimen-related toxicity (RRT) was graded according to the criteria developed by Bearman *et al.* [18].

Supportive therapy

All patients had indwelling multilumen central venous catheter (usually of the Seldinger or Broviac type) and were nursed in steril tents with a laminar flow of HEPA-filtered air. Sterile care and oral as well as gut decontamination were applied. All children received intravenous 7-S immunoglobulins. In the majority of patients rHu-G-CSF was administered starting between day +7 and +10 after transplantation. Irradiated and leukocyte-depleted blood products were given to all children. Since 1995 a pre-emptive treatment with gancyclovir have been used in patients demonstrating reactivation of CMV infection based on weekly CMV-DNA-PCR screening results.

Outcome measures

The outcome measures were: (1) engraftment (ANC ≥ $0{,}5x10^9$/L on three consecutive days and/or platelet count ≥ $20x10^9$/L without transfusion on 7 consecutive days), (2) graft failure (primary failure, i.e. failure to reach ANC ≥ $0{,}5x10^9$/L for at least 28 days after transplantation; secondary failure i.e. decrease of ANC to below $0{,}2x10^9$/L for at least 3 consecutive days after initial engraftment), (3) transplant-related mortality (death in continuous complete remission), (4) acute and chronic GvHD (see above: *Graft-versus-host disease prophylaxis and grading*), (5) leukemia relapse (> 5% blasts in the bone marrow post-transplant), and (6). event-free survival.

Informed consent

The risk related to the treatment procedure was explained in detail to parents and older children, and then informed consent and written agreement were obtained.

Statistical methods

For statistical evaluation of the outcome after BMT, the Kaplan-Meier plots for time-dependent analyses of event-free survival were used.

RESULTS

Engraftment results

In all children sustained engraftment was achieved with a median time to ANC ≥ $0{,}5x10^9$/L of 11 days (range 9 -16), i.e. no primary or secondary graft failure occurred.

Regimen-related toxicity (RRT)

According to the Bearman criteria [18] only mild or moderate expression of RRT was observed with the maximal RRT experienced by, patients of grade II. Toxicity was most common in the gastrointestinal tract, mouth and liver, i.e. gastrointestinal toxicity I^0 – 81,3% (26/32), II^0 – 3,1% (1/32); stomatitis I^0 – 40,3% (13/32), II^0 – 18,8% (6/32); hepatic toxicity I^0 - 28% (9/32); renal, bladder and cardiac toxicity I^0 – 3,1% (1/32).

Acute and chronic GvHD

Acute GvHD grade II-IV was observed in 10 (30,3%) children, while chronic GvHD was diagnosed in 4 (12,5%) patients. In all children acute and/or chronic GvHD resolved after immunosuppressive treatment with CsA and corticosteroids and/or antithymocyte globulin and/or azathioprine.

Transplant-related mortality

No transplant related deaths occurred (TRM = 0%).

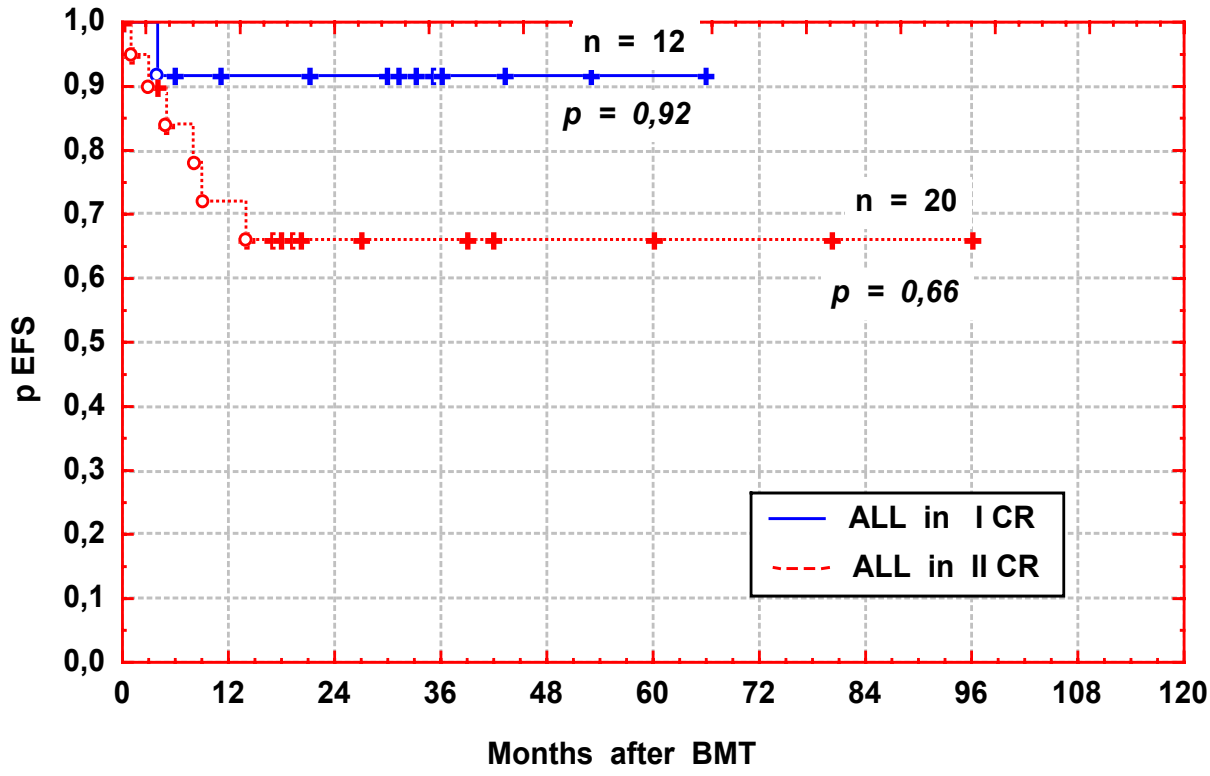

Fig. 1. The probability of event-free survival (pEFS) in children with ALL transplanted in first or second complete remission (CR) after conditioning by fractionated total body irradiation and cyclophosphamide or etoposide.

Leukaemia relapse and event-free survival

Among 12 patients transplanted in I CR only one child relapsed after 4 months from BMT, while the remaining 11 patients are alive in continuous complete remission (CCR) and with a median follow-up of 33 months (range 6 to 66 months) and with 92% probability of a 5-year EFS (*Fig. 1*).

Six of 20 children transplanted in II CR relapsed from 1 to 14 months, from BMT (median 6,5 months). Fourteen of them still remain in CCR with a median of follow-up of 19,5 months (range 1 to 96 months) and with 66% probability of a 8-year EFS (*Fig. 1*).

DISCUSSION

Indications for allogeneic BMT (allo-BMT) and its place in the treatment of childhood ALL should be considered in the context of chemotherapy results. Therefore, the allo-BMT is justified only in those patients with ALL for whom chemotherapy usually fails to be curative, i.e. in 8-10% of children in I CR, who demonstrate factors of a very high risk of chemotherapy failure, such t(9; 22) or t(4; 11), and/or poor prednisone response, and/or no CR at day 33 of induction treatment, and in the majority of children in II or subsequent CR after leukaemia relapse [19,20]. In those children the allogeneic BMT is performed for the consolidation of conventional chemotherapy to improve the overall results of the treatment. However, the treatment failures occur even after allo-BMT and therefore, further optimisation of the transplant procedure is necessary.

In children with ALL the allo-BMT outcome is affected by numerous transplant-related factors, such as donor-recipient HLA-match, source and number of transplanted haematopoietic cells, *in vitro* processing of transplanted material before transplantation, GvHD prophylaxis and GvHD occurrence and supportive therapy [21,22]. However in the context of a rather minor role of graft-versus-leukaemia effect

in ALL [23] the conditioning regimen seems to be the most important factor. Nevertheless, until now it has not been established, which conditioning regimen for BMT in children with ALL assures the best outcome, i.e. the minimum regimen related toxicity along with the maximum anti-leukaemic efficacy.

According to our preliminary observations, the busulfan-based conditioning regimen – despite suggestions by other authors [9] - provided worse results than the total body irradiation (TBI) -containing regimen in children transplanted for ALL in II CR [10]. Recently, this observation has been confirmed in the report of the International Bone Marrow Transplant Registry concerning 176 patients conditioned by BU plus CY and 451 patients who received cyclophosphamide plus TBI from 144 institutions [24]. Besides, Carpenter et al. [25] have demonstrated that the preparative regimen combining BU and CY with single dose melphalan does not lead to a better outcome than that in a control group transplanted using TBI and CY, because of unacceptable toxicity (42% of the children dying of RRT). Increased incidence of a veno-occlusive disease, haemorrhagic cystitis and RRT mortality in children with ALL, especially in patients with advanced leukaemia, who received BU instead of TBI have also been reported by the investigators from the Nordic BMT Group [26].

Therefore, nowadays it is being recommended that children with ALL should be prepared for allo-BMT with TBI-containing regimens. However, further studies are needed on the optimal methods of TBI and its total dose, as well as on chemotherapeutic agents used in preparative regimen in addition to TBI. In our centre since January 1993 all children over 2 years of age suffering from ALL with indications for BMT are conditioned for transplantation by fractionated TBI (FTBI) at a total dose of 12,6 Gy with lung shielding (9,4 Gy) given in 8 fractions during 4 consecutive days (2 fractions/day) plus CY or VP-16. Among 12 patients transplanted for VHR-ALL in I CR only one child relapsed 4 months from BMT, while the remaining 11 patients are alive in CCR with a median follow-up of 33 months (range 6 to 66 months) and with 92% probability of a 5-year EFS. All this proves that in children with VHR-ALL allogeneic BMT performed in I CR is associated with an improved outcome in comparison with the results of conventional treatment alone (30-47% probability of 3-4-year EFS) [4,27]. The role of the myeloablative regimen consisting of TBI plus CY and allogeneic BMT performed in I CR in children suffering from ALL with unfavourable biological features has been demonstrated for the first time in an early report from the French BMT Group [28]. In 32 patients a disease-free survival (DFS) was 84,4% with a median follow-up of 30 months. The investigators from the Nordic BMT Group confirmed a low toxic death rate and a low relapse rate (DFS at 10 years was 73%) in transplant recipients undergoing allogeneic BMT in I CR of high-risk ALL (n = 22) conditioned by TBI and Cy [29]. Recently, preliminary results of prospective study on allogeneic BMT versus chemotherapy for VHR-ALL in I CR conducted by the EBMT Paediatric Working Party and I-BFM-SG have been published [30]. Seven European countries participated in this study, 238 patients received chemotherapy, while 72 patients underwent BMT (45 from HLA identical sibling donors, 20 from unrelated donors, and 12 from alternative family donors). In this study, children were conditioned for BMT by FTBI at a total dose of 12 Gy given in 6 fractions (2 fractions/day) during three consecutive days, followed by VP-16 (60 mg/kg/day). Six (13,3%) of 45 children that underwent allogeneic BMT from HLA identical sibling donors died in CCR as a result of transplant related complications, while leukaemia relapse occurred as a 10 (22,2%) of them. The overall median follow-up was 27 months (range 0-55 months) with 58,4% of DFS probability at 2 years.

In the context of the data from the literature one could conclude that our results are at least comparable or even somewhat better than those reported by other investigators. Therefore, we can recommend a preparative regimen consisting of FTBI of a total dose of 12,6 Gy given in 8 fra-

ctions over 4 days plus VP-16 (60 mg/kg/day) as a well-tolerated regimen and one that demonstrates satisfactory antileukemic efficacy in children with VHR-ALL in I CR. Our group of patients was relatively small, but it was selected according to uniform well-established criteria and uniformly treated at each phase of the procedure, characterized by a relatively long follow-up (up to 66 months, median 33 months).

As already mentioned the conventional regimen consisting of TBI and CY seems superior to the combination of BU and CY in ALL [10,24]. However, no randomised studies have been made to compare the outcome of allogeneic BMT in children with ALL in II CR prepared for transplantation with different FTBI-containing conditioning regimens. Uncontrolled trials using TBI and cytarabine [31], TBI, cytarabine and melphalan [32], and hyper fractionated TBI and CY [33] claim to have reduced the risk of relapse. The substitution of VP-16 for CY in the preparative regimen was studied by the investigators at the City of Hope National Medical Centre in Duarte (California, USA), and it was suggested that the combination of VP-16 and TBI might be associated with a decreased relapse rate in patients with ALL [34,35]. FTBI (12 Gy) and VP-16 (60 mg/kg/day) have also been used by German investigators in 23 children with ALL in II CR [34]. Their data also suggest the reduced relapse rate in these patients (7-year event-free survival 52%, with median follow-up 3,4 years), when compared with those who received TBI and other chemotherapeutic agents (6-year DFS 40 +/- 3%; Barret et al., 1994) [37]. However, further investigation of the contribution of the VP-16 to the outcome is needed to determine if its use reduces post-transplant relapse. At our centre a comparable group of children (n = 20) underwent allogeneic BMT for ALL in II CR. They were prepared for BMT with the same dose of VP-16, i.e. 1 x 60 mg/kg (n = 9) or CY 2 x 60 mg/kg (n = 11), but with a somewhat higher total dose of FTBI, i.e. 12,6 Gy vs 12 Gy given in 8 vs. 6 fractions over 4 vs 3 days. Not a single child died because of transplantrelated complications and the treatment failures observed were exclusively related to leukaemia relapse, which occurred in 6 (30%) patients within 1-14 months (median 6,5 months) from BMT. Fourteen children remain in CCR with a median follow-up of 19,5 months (range 3 to 100 months) and with 66% probability of the a 8-year event-free survival, i.e. the results obtained in our group of patients are at least as good as those reported by German investigators. However, in the context of good tolerance of FTBI in a total dose of 12,6 Gy and its still limited antileukaemic efficacy in children with ALL in II CR, we conclude that the escalation of FTBI total dose from 12,6 Gy to at least 13,2 Gy appears to be justified in those children. In addition, the total dose of FTBI could be individualized according to risk factors of FTBI-related toxicity observed before transplantation, the level of residual disease prior to preparative regimen [36], and the measurements of individual leukaemic cell radiosensitivity [39]. Improvement in the allogeneic BMT outcome in children with ALL will be possible in future if the above measures are taken together with others such as the use of chemotherapeutic agents in preparative regimen according to the results of a drug resistance profile, modulation of drug resistance of residual leukaemic cells, protection and induction of graft-versus-leukaemia effect as well as introduction of adoptive immunotherapy according to quantitative results of molecular monitoring of post-transplant haematopoietic chimerism and minimal residual disease.

REFERENCES

1. Kowalczyk JR. Epidemiologia i etiopatogeneza białaczek. In: Radwańska U (ed.) Białaczki u dzieci. Volumed, Wrocław, 1998;17-39.

2. Radwańska U. Ostra białaczka limfoblastyczna. In: Radwańska U (ed.) Białaczki u dzieci. Volumed, Wrocław, 1998;17-39.

3. Felix CA, Lange BJ, Chessells JM. Pediatric acute lymphoblastic leukemia: challenges and controversies in 2000. „Hematology 2000" - Am Soc Hematol Educ Program, San Francisco, 1-5 grudnia 2000; 285-302.

4. Schrappe M, Camitta B, Pui C-H, Eden T, Gaynon P, Gustafsson G, et al. Long-term results of large pros-pective trials in childhood acute lymphobla-stic leukemia. Leukemia 2000;14:2193-4.

5. Chessels JC. Relapsed acute lymphoblastic leukemia: bone marrow transplant or conventional treatment? In: „Hematology 2000" - Am Soc Hematol Educ Program, San Francisco, 1-5th December 2000,291-4.

6. Chybicka A, Bogusławska-Jaworska J, Gorczyńska E, et al. Wstępne wyniki leczenia I nawrotu ostrej białaczki limfoblastycznej wg programu BFM 96 u dzieci w materiale Polskiej Pediatrycznej Grupy ds. Leczenia Białaczek i Chłoniaków. Med. Wieku Rozw 2000;4 (suppl 2):43-8.

7. Niethammer D. Childhood leukaemias. Oncol Rev 1996;11:15-6.

8. Wachowiak J, Bogusławska-Jaworska J, Kowalczyk JR, et al. Hematopoietic stem cell transplantation in Polish pediatric centers – development and current status. Med Sci Monitor 2000;6 (suppl. 2):4.

9. Tutschka PJ, Copelan EA, Klein JP: Bone marrow transplantation for leukemia following a new busulfan and cyclophosphamide regimens. Blood 1987;70:1382-8.

10. Wachowiak J, Bettoni C, Lange A, Malicki J, Kaczmarek-Kanda M, Głuszak B, et al. Can busulfan replace fractionated total body irradiation as conditioning regimen for allogeneic bone marrow transplantation in children with acute lymphoblastic leukemia? Acta Haematol Pol 1995;26: 377-84.

11. Skoczeń S, Klus K, Armata J, Kowalczyk J, Jackowska T, Wiśniewska-Ślusarz H, Kolecki P, et al. High risk acute lymphoblastic leukaemia in children. Preliminary report after introducing a new version of New York (1997) protocol adjusted to the age of the patients – report of the Polish Paediatric Leukaemia/Lymphoma Study Group. Med Wieku Rozwoj 2000; 4 (suppl. 2):23-32.

12. Bogusławska-Jaworska J, Chybicka A, Strzelczyk R, et al. Sześcioletnie doświadczenia w leczeniu pierwszego nawrotu ostrej białaczki limfoblastycznej u dzieci w materiale Polskiej Grupy Pediatrycznej ds. Leczenia Białaczek i Chłoniaków. Ped Pol 1994;69:711-9.

13. Malicki J. The accuracy of dose determination during total body irradiation. Strahlenther Onkol 1999;175:492-6.

14. Malicki J, Wachowiak J, Kosicka G, Stryczyńska G, Nowak A, Pracz J. Total body irradiation before bone marrow transplantation: aims and results. Adv Exp Med Biol 2001;495:277-82.

15. Malicki J, Kosicka G, Stryczyńska G, Wachowiak J. Cobalt 60 versus 15 MeV photons during total body irradiation: doses in the critical organs and complexity of the procedure. Ann Transplant 2001;6: 18-22.

16. Glucksberg H, Storb R, Fefer A, Buckner CD, Neiman PE, Lerner KG, et al. Clinical manifestatios of graft-versus-host disease in human recipients of marrow from HLA matched sibling donors. Transplantation 1974;18:295-304.

17. Schulman HM, Sullivan KM, Weiden PL, Witherspoon RP, Mc Donald GB, Schubert MM, et al. Chronic graft- versus-host disease syndrome in man. A long term clinical pathological study of 20 Seattle patients. Am J Med 1980;69:204-12.

18. Bearman SL, Appelbaum FR, Buckner CD, Petersen FB, Fisher LD, Clift RA, et al. Regimen-related toxicities in patients undergoing bone marrow transplantation. J Clin Oncol 1988;6:1562-8.

19. Davies SM, Ramsay NKC, Kersey JH. Allogeneic transplantation for acute lymphoblastic leukemia in children. In: Hematopoietic cell transplantation. Red. Thomas ED, Blume KG, Forman SJ. Blackwell Science, Malden, 1999;859-71.

20. Goldman JM, Schmitz N, Niethammer D, et al. Allogeneic and autologous transplantation for haematological diseases, solid tumors and immune disorders: current practice in Europe in 1998. Bone Marrow Transplant 1998;21:1-7.

21. Barret AJ, Horowitz MM, Gale RP, et al. Marrow Transplantation for acute lymphoblastic leukemia: factors affecting relapse and survival. Blood 1989;74:862-71.

22. Weisdorf DJ, Woods WG, Nesbit ME, et al. Allogeneic bone marrow transplantation for acute lymphoblastic leukemia: risk factors and clinical outcome. Br J Haematol 1994;86:62-9.

23. Collins RH, Goldstein S, Giralt S, et al. Donor leukocyte infusions in acute lymphocytic leukemia. Bone Marrow Transplant 2000;26:511-6.

24. Davies SM, Ramsay NKC, Klein JP, Weisdorf DJ, Bolwell B, Cahn JY, et al. Comparison of preparative regimens in transplants for children with acute lymphoblastic leukemia. J Clin Oncol 2000; 18:340-7.

25. Carpenter PA, Marshall GM, Giri N, Vowels MR, Russell SJ. Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia conditioned with busulfan, cyclophosphamide and melphalan. Bone Marrow Transplant 1996;18: 489-94.

26. Ringden O, Ruutu T, Remberger M, Nikoskelainen J, Volin L, Vindelor L, et al. A randomized trial comparing busulfan with total body irradiation as conditioning in allogeneic marrow transplant recipients with leukemia: A report from the Nordic Bone Marrow Transplant Group. Blood 1994;83:2723-30.

27. Pui CH, Evans WE. Acute lymphoblastic leukaemia. N Engl J Med 1998;339: 605-15.

28. Bordigoni P, Vernant JP, Souillet G, Gluckman E, Marininchi D, Milpied N, et al. Allogeneic bone marrow transplantation for children with acute lymphoblastic leukemia in first remission: a cooperative study of the Groupe d'Etude de la greffe de Moelle Osseuse. J Clin Oncol 1989;7: 747-53.

29. Saarinen UM, Mellander L, Nysom K, Rindgen O, Schroeder H, Glomstein A, et al. Allogeneic bone marrow transplantation in first remission for children with very high-risk acute lymphoblastic leukemia: a retrospective case-control study in the Nordic countries. Bone Marrow Transplant. 1996;17:357-63.

30. Uderzo C, Balduzzi A, De Lorenzo P, Valsecchi MG, Gadner H, Klingebiel T, et al. Prospective study on allogeneic bone marrow transplantation (AlloBMT) versus chemotherapy (Chemo) for very high-risk (VHR) childhood acute lymphoblastic leukaemia in first complete remission. Bone Marrow Transplant 2001;28 (suppl. 1):22-4.

31. Weyman C, Graham-Pole J, Emerson S, August C, Champlin R, Coccia P, et al. Use of cytosine arabinoside and total body irradiation as conditioning for allogeneic marrow transplantation in patients with acute lymphoblastic leukemia: a multicenter survey. Bone Marrow Transplant 1993;11:43-50.

32. Bordigoni P, Esperou H, Souillet G, Pico J, Michel G, Laccur B, et al. Total body irradiation-high-dose cytosine arabinoside and melphalan followed by allogeneic bone marrow transplantation from HLA-identical siblings in the treatment of children with acute lymphoblastic leukemia after relapse while receiving chemo-therapy: a Societe Francaise de Greffe de Moelle study. Br J Haematol 1998;102:656-62.

33. Boulad F, Steinherz P, Reyes B, Heller G, Gillio AP, Small TN, et al. Allogeneic bone marrow transplantation versus chemotherapy for the treatment of childhood acute lymphoblastic leukemia in second remission: a single-institution study. J Clin Oncol 1999;17:197-202.

34. Blume KG, Forman SJ, O'Donnell MR, Doroshow JH, Krance RA, Nademane AP, et al. Total body irradiation and high-dose etoposide: a new preparatory regimen for bone marrow transplantation in patients with advanced hematologic malignencies. Blood, 1987;69:1015-20.

35. Schmitz N, Gassmann W, Rister M, Johannson W, Sottorp M, Brix F, et al. Fractionated total body irradiation and high-dose VP 16-213 followed by allogeneic bone marrow transplantation in advanced leukemias. Blood, 1988;72:1567-73.

36. Dopfer R, Henze G, Bender-Götze C, Ebell W, Ehninger G, Friedrich W, et al. Allogeneic bone marrow transplantation for childhood acute lymphoblastic leukemia in second remission after intensive primary and relapse therapy according to the BFM- and CoALL-Protocols: Results of the German Cooperative Study. Blood, 1991;78: 2780-4.

37. Barret AJ, Horowitz MM, Pollock BH, Zhang NJ, Bortim MM, Buchanan GR, et al. Bone marrow transplants from HLA-identical siblings as compared with chemotherapy for children with acute lymphoblastic leukemia in a second remission. N Engl J Med 1994;331:1253-8.

38. Knechtli CJ, Goulden NJ, Hancock JP, Grandage VL, Harris EL, Garland RJ, et al. Minimal residual disease status before allogeneic bone marrow transplantation is an important determinant of successful outcome for children and adolescents with acute lymphoblastic leukemia. Blood 1998; 92:4072-9.

39. Wheldon TE, Barrett A. Radiobiological modelling of the treatment of leukaemia by total body irradiation. Radiother Oncol 2001;58:227-33.