AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPLANTATION IN CHILDHOOD SOLID TUMOURS

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Despite overall improvements in the prognosis for childhood malignancies children with primary metastatic or relapsed tumours are not likely to be cured with a conventional combined therapy. In such patients, the EFS rate at 3yrs remains less than 30%. Solid tumours in children, such as neuroblastoma, rhabdomyosarcoma, Ewing's tumour, Wilm's tumour and germ cell tumour are all chemotherapy sensitive and exhibit a dose-response relationship to therapy with selected agents like alkylating agents, irradiation, anthracyclines, vinca alkaloids, anti-metabolites and topoisomerase inhibitors [1]. For agents whose major dose limiting toxicity is myelosuppression, haematopoietic stem cell (HSC) rescue may permit 3-10x dose escalation before nonhaematopoietic toxicity becomes dose limiting and combination of three or more non-cross resistant drugs at full or nearly full doses has a curative potential. Therefore, several groups have developed regimens to exploit the steep dose response curves by using stem cell rescue to circumvent the dose-limiting haematopoietic toxicity.

NEUROBLASTOMA

Neuroblastoma (NBL) is the commonest and best studied pediatric solid tumours. This disease is a particulary good candidate for high dose strategies: it is sensitive to chemotherapy and radiation and for most patients present with a disseminated disease for which conventional chemotherapy produces less than a 20% chance for a long term survival. However, only two randomized studies have been reported so far. The study by Pinkerton et al. demonstrated an advantage of consolidation with high dose melphalan and bone marrow rescue over no further therapy [2]. The Children's Cancer Group has made a large randomized comparison of high dose carboplatin-melphalan-VP16 and total body irradiation (TBI) with autologous, purged bone marrow (BM) rescue as consolidation vs. no further therapy in children with high risk neuroblastoma. All patients who completed cytotoxic therapy without disease progression were then randomly assigned to receive no further therapy or treatment with 13-cis-retinoic acid for six months. The final analysis has demonstrated a significantly better event-free survival (EFS) in children who received high dose therapy (HDT) [3]. In the second randomization, the group treated with 13-cis fared better than pts with no further therapy. The most significant difference was that between patients (pts) with HDT and retinoic acid vs. conventional chemotherapy (only - 55% vs. 18% EFS-rate). This randomized study demonstrates for the first time that HDT is beneficial for patients with NBL, and that additional therapy with retinoic acid further improves survival.

Many cooperative groups carried out several non-randomized trials. Their results must be regarded as suggestive rather than definitive since without randomization, unknown selection factors may bias the comparison. The results of these small studies differed sigificantly. McCowage reported an EFS rate of 87% at 5 yrs in 28 children older than 1 yr of age, and Stage IV NBL treated with teniposide, melpahalan, cisplatin and TBI with non-purged BM reinfusion as rescue [4]. Dini et al. achieved a 29% progression-free survival rate in 34 patients (aged 1-7 yrs) with resistant or relapsed and primary metastatic NBL treated with a regimen including vincristine, fractionated TBI and melphalan. Unpurged BM was used as rescue [5]. Since many biological and other therapy related factors may influence the prognosis, it is not possible to draw a definitive conclusion from these studies.

The European Group for Blood and Marrow Transplant Registry provides sufficient data in order to evaluate the survival of a large cohort of children with NBL who were treated with

HDT at different European centers. Even though treatment modalities differed between centers and countries, the large number of patients included in the analysis partially compensated for this disadvantage.

Philip et al. reported on 1070 myeloablative procedures followed by stem cell rescue as either BM or PBSC [6]. The overall survival (OS) was 49 % at 3 yrs, and 33% at 5 yrs, which confirmed previous findings that HDT shifts the survival curve to the right, i.e. prolongs survival without a significant effect on the definitive cure rate. It is worth noting that the matched pair comparison of 17 allogeneic and 34 autologous transplantation did not reveal any difference. Persisting bone (99Tc and /or mIBG scan positive) and bone marrow involvement after induction treatment were the major negative prognostic factors [7]. There was no difference between high dose therapy incorporating TBI and chemotherapy alone. There was no significant difference in prognosis between single and double HDT.

A French group conducted a nonrandomized pilot study (LMCE2) using a double harvest/double graft approach with two different HDT regimens: tenoposid, carmustine, cisplatinum (or carboplatin), and vincristin, melphalan and TBI. The first harvest was scheduled 4 weeks after the last chemotherapy, the second one 60-90 days after HDT. The marrow was purged *in vitro* by an immunomagnetic technique. The OS values at 2 yrs and 5 yrs were 36% and 32% respectively. The toxic rate was very high at 24%, which was probably due to the delayed engraftement related in part to the BM-harvesting after 1. HDC [8]. In the subsequent study of this group (LMCE3), a HDT (vincristine, melphalan and fractionated TBI) was given as consolidation in pts who were in complete remission after induction therapy. Purged BM was used as rescue. The progression-free survival rate was 29% at 7 yrs [9]. Data derived from two concurrent Children`s Cancer Group Studies suggested that consolidation with myeloablative chemoradiotherapy and autologous BMT was more effective than continued multiple courses of chemotherapy, especially in patients with MYCN amplified neuroblastoma. EFS rate for patients with MYCN amplified tumours was 67% [10]. The results published by Kawa et al. also indicate an advantage for HDT only in pts who have MYCN amplified tumours [11]. These data point to the need to identify subgroups, since the relative efficacy of myeloablative and non-myeloablative therapy may vary, depending on the biological characteristic of the tumour subgroup.

There is a small but very promising single institution study published by Klingebiel et al. [12]. The patients were treated according to the German Neuroblastoma Trial NB 90 and then consolidated with [131 I-m]IBG (0.58 GBq/kg) prior to the HDT, which consisted of melphalan, carboplatin and etoposide. The rescue consisted of highly purified autologous peripheral progenitor cells. After haematopoietic reconstitution immuntherapy with anti-GD2 murin or chimeric antibodies (ch14.18) was administered. Nine out of eleven children are alive disease free with a median observation time of 19 months.

An important contribution to the assessment of the role of HDT in pts with NBL is the analysis of the German NBL 90 Study. Patients with Stage IV NB received either HDT (melphalan, etoposide, carboplatin) or twelve alternating cycles of oral melphalan/etoposide and oral cyclophosphamide and vincristine. Forty - three pts received HDT and 68 were on maintanance therapy. The progression-free survival (PFS) was 30% for the group of patients (68 pts) receiving maintenance therapy, compared with 27% for the HDT group (43 pts) [13].

It seems that HDT might be beneficial for selected patients with NBL (older than 2 yrs, MYCN amplified tumours), but the timing, type of conditioning and of rescue important for definitive cure remain to be defined.

EWING`S FAMILY OF TUMOURS

Ewing`s tumors (Ewing`s sarcoma and peripheral neuroectodermal tumour) are sensitive to radio- and chemotherapy. However, patients with bone and bone marrow metastases, pelvis primary and early relapse have a dismal prognosis. In these patients, the dose escalation was thought to improve prognosis. Unfortunately, no randomized trial has been conducted so far. Several studies on small series of patients have been published. Burdach et al. reported on a group of 17 patients with metastatic or relapsed Ewing`s sarcoma, who were treated with hyperfractionated TBI and HDT consisting of melphalan and etoposide with or without carboplatin [14]. The probability of a relapse at 6 yrs was 52%. However, these very good results have not been confirmed by subsequent trials. Laws et al. reported 6 yrs later on 25 patients with poor prognosis Ewing` sarcoma, who were treated with similar HDT (TBI followed by melphalan and etoposide). The EFS-rate was 34%. The patients received IL2 as immunmodulation after HDT [15]. The analysis of 171 pts with primary metastatic Ewing`s tumour treated according to the

EICESS studies revealed, however, that in pts with combined lung and skeletal metastases, a consolidation with HDT and/or whole lung irradiation improved EFS from 0% to 27% [16].

The French Society of Pediatric Oncology (SFOP) examined the efficacy of busulfan and melphalan given as a consolidation to patients with metastatic Ewing's sarcomas. The EFS and overall survival (OS) rate at 3 yrs were 52% and 76%, resepectively. These results compared favourably with those observed after treatment with conventional chemotherapy alone [17]. The National Cancer Institute conducted three trials (1981 until 1986), which were designed to determine whether TBI administered as consolidation therapy would improve the prognosis in high risk Ewing's sarcoma patients. With a minimum follow-up of 6 yrs, it has become clear that this approach has not improved the prognosis in this group of patients [18].

The retrospective multivariate analysis of the data from the registry of the EBMT Solid Tumour Working Party revealed several important facts concerning HDT in Ewing' tumours [19]. The OS in 411 patients registered was 30%. In 219 pts, the data were complete so a multivariate analysis was performed. The group who received a busulfan containing regimen had a superior OS rate of 41% in comparison with the group who received a TBI containing regimen (14%). A matched pair analysis based on primary tumour sites, type of metastases at diagnosis, status prior to HDT and organs involved at HDT comparing TBI versus busulfan regimens was in favour of busulfan regimens (OS at 5 yrs BU 28% versus TBI 11%, p=0.04).
Based on these results, busulfan and melphalan containing HDC will be examined in a randomized fashion in the new Euro-E.W.I.N.G.99 protocol.

RHABDOMYOSARCOMA

The prognosis of patients with localised tumours treated according to the cooperative studies in Europe and USA has improved in the last 20 years, with survival rates of approximately 70%. In contrast, the chance of cure in primary metastatic or relapsed tumours is very poor [20,21]. The prognostic relevant factors in pts with primary metastatic tumors treated according to the CWS-Studies -81, -86 and -91 were: 1. age (>10 yrs), 2. alveolar histology, 3. more than one metastatic site and/or bone/bone marrow metastases. Pts with Stage IV and no risk factors had an EFS rate at 5 yrs of 31%, with one risk factor 22% and with >2 risk factors 2% (p<0.000). Since RMS is a chemosensitive tumour the escalation of dose intensity seemed to be the best way of improving the results.

A retrospective analysis of the German/Austrian Pediatric Bone Marrow Transplantation Group Registry revealed 36 pts with primary metastatic or relapsed rhabdomyosarcoma (RMS) who were given HDC±TBI and HR rescue [21]. Primary therapy was given according to CWS-Studies or the European MMT Stage IV Study. The HDT consisted of fractionated melphalan 4x 30-45mg/m^2, etoposide 40-60mg/kg, carboplatin 3 x 400-500 mg/m^2 in 26 pts. 10 pts received additional fractionated TBI. Seven pts were treated with melphalan alone or in combination with carboplatin. Two patients received cyclophosphamide/busulfan with TLI (total lymphoid irradiation) and 1 cyclophosphamide with FTBI. Thirty - three patients were given autologous BM or peripheral blood stem cells (PBSC) as hematopoietic rescue and five were given allogeneic bone marrow. Ten patients received adjuvant IL2. There was one toxic HDC-related death. Ten patients were alive free of disease with a median observation time of 43 months (23-92), and two patients were alive with evidence of the disease. The tumour recurred in the majority of patients at previously known sites, in 5 cases new metastatic sites were observed. The patients with primary localised tumours who had been treated with HDT because of a relapse did better (4 of 9 alive disease free) than patients with primary metastatic disease (5 of 27 alive disease free). This analysis did not show any benefit from HDT, as late consolidation after standard chemotherapy and local therapy in pts with poor risk RMS.

In the European MMT Stage IV Study 52 of 175 eligible pts with Stage IV RMS received melphalan as a late consolidation after achieving CR. The respective 3 yrs EFS and OS rate were 29.7% and 40%, compared with 19.2% and 27.7, in those receiving standard chemotherapy [22].

The analysis of pts with RMS registered in the EBMT registry provides information on HDT with HR administered by several investigators participating in the EBMT group for children and young adults with RMS [23, 24, 25, 26]: 418 pts diagnosed between 1979 and 1997 were analysed. The median age at diagnosis was 9.2 yrs (<1-41). The indication for HDT was a primary metastatic disease (157 pts) or relapse/progression of a primary localised tumour (261 pts). The first line therapy was given for majority of patients according to different European studies between 1979 and 1997, i.e. SIOP Studies,

Italian (AIEOP, ICG) and German (CWS) studies. 363 patients received one HDT, 50 double and 5 triple. 57 % of pts were in CR before HDT, the remainder had a macroscopic tumour mass. The proportion of patients alive who received HDT in 1.CR (164) or 2.CR (74) did not differ and was 36%. In the majority of pts the HDT contained melphalan either alone (23%) or in combination with etoposide, carboplatin, cyclophosphamid, BCNU and vincristin (47%). The median time from the last event to the first HDT ranged between 8-9 months and did not differ dependent on the indication for HDT. There was no major difference at the outcome according to the indication for HDT: 28% pts with primary metastatic RMS are alive in comparison to 35% with other indications (relapse or primary metastatic) for HDT. The rate of toxic death was 9% and 5% respectively. There was a difference in prognosis between primary metastatic and other pts dependent on the number of HDT. The best group with 41% patients alive consisted of pts with a relapsed or resistant disease with double HDT. In contrast, pts who received double HDT because of primary metastatic tumour had the worst prognosis, only 11% being alive.

Patients diagnosed between 1989 and 1997 had a significant better chance of survival: 38% vs. 14%, as compared with patients diagnosed earlier, i.e. in the period of 1979-1988. The main reason for the better outcome was the dramatical improvement in the rate of fatal toxicities 16% vs. 2%.

What is interesting is the fact that the median time from the last HDT to tumour-death was very short 9 months in all pts. The difference between pts in CR before HDT and those not achieving a CR was only about 2 months. The median time to toxic death was very short: 1,5 months. These data show that what one considers as CR probably does not represent a remission, and the growth dynamic of tumour cells that survived HDC is very high. In conclusion: patients with high risk RMS treated in the last 10 years in different European centers seem to have gained some benefit from HDT. Since the progression of the disease occured very quickly after HDT the question arises it there is a negative selection of very malignant clones or whether the immundeficiency after HDT contributes to the rapid growth of the residual tumour. Therefore, it seems most likely that a some kind of immunmodulation after HDT is needed.

The German Soft Tissue Sarcoma Study HD-CWS 96 has compared the efficacy of double HDT versus an oral maintanance therapy as a consolidation therapy in patients with primary metastatic rhabdomyosarcoma-like soft tissue sarcoma [27]. High dose treatment consisted of a tandem cycle of thiotepa (600 mg/m^2) + cyclophosphamide (4500 mg/m^2) and melphalan (120 mg/m^2) + etoposide (1800 mg/m^2). The maintanance therapy consisted of trofosfamid (10 days 150 mg/m^2/day) + etoposide (10 days 50 mg/m^2/day) and trofosfamid (10 days 150 mg/^{2}/d) + idarubicin (4 x 5 mg/m^2/d). In the high dose group only 3/22 remained progression-free, whereas 6/11 orally treated patients.

These data showed that HDT in poor prognosis rhabdomyosarcoma cannot be regarded as an established therapy leading to a better prognosis and should be performed in prospective controlled trials only.

WILMS` TUMOUR

The prognosis for pts with Wilms` tumour even with a primary metastatic disease is very, good so the experience with HDT is very limited. There are, however, still primary metastatic or recurrent tumours which cannot be controlled by conventional chemotherapy. Dallorso et al. have analysed pts with poor risk Wilms` tumour registered in the EBMT registry: 81 received melphalan based HDT [28]. The tumour status before HDT was very heterogenous, CR, PR and even RR. The overall disease-free survival from HDT was 57% and for pts in CR before HDT 78%.

The SFOP has conducted the first prospective study trial on HDT for high-risk relapsed Wilms` tumour. The EFS at 3 yrs was 50% [29]. So in conclusion: there is no statistically proved benefit from HDT in Wilms` tumour, but the EBMT and SFOP results are sufficiently encouraging to warrant prospective evaluation.

BRAIN TUMOURS

Brain tumours are the second most frequent neoplasms in children. Despite advances in surgery, chemotherapy and radiotherapy, cure rates for children with malignant brain tumours remain modest. The prognosis for recurrent brain tumours is dismal. The role of HDT in brain tumours is based on the premise that they are sensitive to alkylator-based chemotherapy and show a steep dose-response curve. Several studies have been published in children with brain tumours who received HDT as a salvage in a primary poor risk or relapsed disease.

In 1996 Mahoney et al published the results of a multicenter POG study for children with recurrent or progressive brain tumors (medulloblastoma, ependymoma, glioma, PNET) [30]. The HDT consisted of increasing

doses of cyclophosphamid administered sequentially with melphalan. BM was given as rescue: 19 children were enrolled on this study. All these patients had been previously treated with cranial or craniospinal radiotherapy: 17 of 18 pts having measurable disease at the time of HDT. There was a high TRM: 22%. 39% pts achieved a complete response, EFS at one 1yr was 39%.

In a multicentric study published by Graham et al. 49 pts with recurrent or poor prognosis brain tumours (medulloblastoma, glioblastoma, ependymoma, germ cell, PNET) were treated with HDT consisting of busulfan, melphalan, carboplatin and etoposide [31]. BM was given as rescue. Only one therapy related death was noted and 18 pts were disease free at 22-55 months after HDT. It was concluded that some pts may benefit from such an approach.

Gururangan et al. reported on 20 patients with recurrent malignant brain tumours (medulloblastoma, glioblastoma, PNET, pinealoblastoma) treated with the HDT that consisted of different combination of carboplatin, thiotepa, etoposide, and carmustine (BCNU). Autologous BM was used as rescue. Twelve patients received radiotherapy 6 weeks post-HDT. The EFS at 3 yrs was 47% [32]. Therapy related mortality was 10%. This study shows that HDT followed by RTX may be an effective therapy for some children with recurrent brain tumours.

The prospective assessment of HDT in children with diffuse pontine gliomas has been made by SFOP. HDT consisting of busulfan and thiotepa was initiated 40-60 days after radiotherapy: 36 pts were included in the study. No benefit from this aggressive treatment was seen [33].

CONCLUSIONS AND FUTURE PERSPECTIVES

HDT improves the degree of tumour volume reduction and consenquently prolongs EFS and OS. There is no proved benefit of HDT for cure rates. Since fatal toxicities have been reduced by a better supportive care and the use of highly purified HSC, the HDT can be used in the future as a kind of consolidation therapy, followed by maintenance therapies such as stimulation of differentiation, anti-angiogenesis, or immunmodulation for eradication of a microscopic disease. There are still, however, a number of unanswered questions with regard to HDT. The best conditioning regimen has yet to be found. Another question is whether there is a preferred rescue product. Autologous peripheral mobilized cells are now thought to be the best source of haematopoietic rescue. PBSC produce more rapid engraftment than bone marrow, which in turn leads to decreased toxicity of HDT. Nevertheless the question of whether the purging of autologous grafts can improve the outcome remains to be answered. Based on the results of gene marking studies it is now apparent that neuroblastoma cells contaminating the grafts can contribute to relapse. However, retrospective analyses have not demonstrated a significant reduction in the risk of relapse by purging. The contamination with tumour cells remains, however, as a major problem. The methodology of a positive selection of CD34 positive cells has been established. It is possible, however, that some tumour cells do express CD34 antigens, and, as a result, are present in the CD34 positive products. The absence of a benefit from allogeneic bone marrow transplantation indicates that tumour contamination of the autologous grafts did not contribute to large number of relapses, and that alloreactive cytotoxic T lymphocytes are not substantially effective against solid tumous. Graft versus tumour effects are well documented after allogeneic transplantation for haematologic malignancies. Due to a major progress and evolution in the field of allogeneic transplantation allogeneic stem cells became now a very interesting alternative as a therapy modality in patients with solid tumours. There is some evidence now that a graft vs. tumour effect can be established.

A possible concept for the future could employ conventional therapy with local therapy as induction and consolidation with HDT and stem cell rescue followed by tumour specific peptide vaccination with autologous dendritic and T cell transplantation or allogeneic cell mediated therapy, i.e. by induction of mixed chimerism and anti-tumour effects.

REFERENCES

1. Chen AR. High dose therapy with stem cell rescue for pediatric solid tumors:rationale and results. Pediatr Transplantation 1999; 3, suppl.1: 78-86.

2. Pinkerton CR. ENSG 1 randomized study o high dose melphalan in neuroblastoma. Bone Marrow Transplant 1991; 7: 112-3.

3. Matthay KK, Villablanca JG, Seeger RC, et al. Treatment of high-risk neuroblastoma with intensive chemotherapy, radiotherapy, autologous bone marrow transplantation, and 13-cis-retinoic acid. N Engl J Med 1999; 341: 1165-73.

4. McCowage GB, Vowels MR, Shaw PJ, et al Autologous bone marrow transplantation for advanced neuroblastoma using teniposide, doxorubicine, melphalan, cisplatin and total body irradiation J Clin Oncol 1995; 13: 2789-95.

5. Dini G, Lanino E, Garaventa AD, et al Myeloablative therapy and unpurged autologous bone marrwo transplantation for poor-prognosis neuroblastoma: report of 34 cases. J Clin Oncol 1991; 9: 962-9.

6. Philip T, Ladenstein R, Lasset CO. 1070 Myeloablative megatherapy procedures followed by stem cell rescue for neuroblastoma: 17 years of European experience and conclusions. European Group for Blood and Marrow Registry Solid Tumor Working Party. Eur J Cancer 1997; 33: 2130-5.

7. Ladenstein R, Philip T, Lasset CO, et al. Multivariate analysis of risk factors in stage 4 neuroblastoma patients over the age of one year treated with megatherapy and stem-cell transplantation: a report from the European Bone Marrow Transplantation Solid Tumor Registry J Clin Oncol 1998; 16: 953-65.

8. Philip T, Ladenstein R, Zucker JM, et al. Double megatherapy and autologous bone marrow transplantation for advanced neuroblastoma: the LMCE2 study Br J Cancer 1993; 67: 119-27.

9. Frappaz D, Michon J, Coze C, et al. LMCE3 treatment strategy: results in 99 consecutively diagnosed stage 4 neuroblastoma in children older than 1 year at diagnosis J Clin Oncol 2000; 18: 468-76.

10. Stram DO, Matthay KK, O`Leary M, et al. Consolidation chemoradiothreapy and autologous bone marrow transplantation versus continued chemotherapy for metastatic neuroblastoma: a report of two concurrent Children`s Cancer Group Studies J Clin Oncol 1996; 14: 2417-26.

11. Kawa K, Ohnuma N, Kaneka M, et al. Long-term survivors of advanced neuroblastoma with MYCN amplification: A report of 19 patients surviving disease-free for more than 66 months. J Clin Oncol 1999; 17: 3216-20.

12. Klingebiel Th, Bader P, Beck J, et al. Treatment of neuroblastoma stage 4 with 131I-meta-iodo-benzylguanidine, high-dose chemotherapy and immuntherapy. A Pilot study. Eur J Cancer 1998; 34: 1398-402.

13. Kremens B, Hero B, Garte M, et al. Maintenance therapy versus megatherapy as consolidation treatment in stage 4 neuroblastoma Med Pediatr Oncol 1996; 27: 251.

14. Burdach St, Jürgens H, Peters C, et al. Myeloablative radiochemotherapy and hematopoietic stem cell rescue in poor prognosis Ewing sarcoma. J Clin Oncol 1993; 11: 1482-8.

15. Laws HJ, Burdach S, van Kaick B, et al. Multimodality diagnostics and megatherapy in poor prognosis Ewing`s tumor patients. A single-center report. Strahlenther Onkol 1999; 175: 488-94.

16. Paulussen M, Ahrens S, Burdach S, Craft A, Dockhorn-Dworniczak B, Dunst J, Fröhlich B, Winkelmann W, Zoubek A, Jürgens H. Primary metastatic (stage IV) Ewing tumor: survival analysis of 171 patients from the EICESS studies Ann Oncol 1998; 9: 275-81.

17. Valteau-Couanet D, Michon J, Plouvier ED, et al. Treatment of metastatic Ewings`s sarcomas with busulfan and melphalan consolidation high dose chemotherapy. A study of the French Society of Pediatric Oncology (SFOP) Med Pediatr Oncol 1999; 27: 238.

18. Horowitz ME, Kinsella TJ, Wexler LH, et al. Total body irradiation and autologous bobe marrow transplant in the treatment of high risk Ewing`s sarcoma and rhabdomyosarcoma J Clin Oncol 1993; 11: 1911-8.

19. Ladenstein R, Hartmann O, Pinkerton R, et al. A multivariate and matched pair analysis on high risk Ewing` tumor patients undergoing mgt/scr in Europe. Bone Marrow Transplant 1999; 21: 227.

20. Klingebiel Th, Pertl U, Hess CF, et al. Treatment of children with relapsed soft tissue sarcoma: Report of ethe German CESS/CWS REZ 91 Trial. Med Pediatr Oncol 1998; 30: 269-75.

21. Koscielniak E, Klingebiel T, Peters C, et al. Do patients with metastatic and recurrent rhabdomyosarcoma benefit from high-dose therapy with hematopoietic rescue? Report of the German/ /Austrian Pediatric Bone Marrow Transplantation Group. Bone Marrow Transplant 1997; 19: 227-31.

22. Carli M, Colombatti O, Oberlin O, et al. High – dose melphalan with autologous stem-cell rescu in metastatic rhabdomyosarcoma. J Clin Oncol 1999; 17: 2796-803.

23. Koscielniak E, Rosti G, Treuner J, et al. Prognosis in patients with primary bone and/or bone marrow metastases of rhabdomyosarcoma (RMS). A joint report of the EBMT Solid Tumor Working Party and the German Soft Tissue Sarcoma Study (CWS). Bone Marrow Transpl. 1998; 21: 226.

24. Koscielniak E, Rosti G, Hartmann O, et al. 20 yrs experience with high dose chemotherapy in patients with metastatic and recurrent rhabdomyo-sarcoma. An EBMT Solid Tumor Working Party update 1998, Bone Marrow Transplant 1999; 23: 190.

25. Koscielniak E, Harms D, Henze G, et al. Results of treatment for soft tissues sarcoma in childhood and adolescence. A final report of the German Cooperative Soft Tissues Sarcoma Study CWS-86. J Clin Oncol 1999; 17: 3706-19.

26. Koscielniak E, Rosti G, Hartmann O, et al. Is more better? Double high dose chemotherapy in patients with metastatic and recurrent rhabdomyosarcoma. Bone Marrow Transplant 2000; 25: 69.

27. Klingebiel, Koscielniak E, PilzT, et al. High dose therapy versus oral maintance: Interim result of HD CWS 96 study for tretament of patients with metastasized soft tissue sarcoma. Bone Marrow Transplant 2000; 25: 245.

28. Dallorso S, Badel-Serra I, Baranzelli MC, et al. High dose therapy (HDT) with stem cell rescue in poor risk Wilms' tumor: an EBMT solid tumor wp rgistry update at June 1997. Bone Marrow Transplant 1998; 21: 230.

29. Pein F, Michon J, Valteau-Couanet D, et al. High – dose melphalan, etoposide, and carboplatin followed by autologous stem – cell rescue in pe recurrent Wilm's tumor: a French Society of Pediatric Oncology study. J Clin Oncol 1998; 16: 3295-301.

30. Mahoney DH, Strother D, Camitta B, et al. High dose melphalan and cyclophosphamid with bone marrow rescue for recurrent/ progressive malignant brain tumros in children: A Pilot Pediatric Oncology Group Study J Clin Oncol 1996; 14: 382-8.

31. Graham ML, Herndon JE, Casey IIJR, et al. High dose chemotherapy with autologous stem-cell rescue in patients with recurrent and high risk pediatric brain tumors. J Clin Oncol 1997; 15: 1814-23.

32. Gururangan S, Dunkel IJ, Goldman S, et al. Myeloablative chemotherapy with autologous bone marrow rescue in young children with recurrent malignant brain tumors. J Clin Oncol 1998; 16: 2486-93.

33. Bouffet E, Raquin M, Doz F, et al. Radiotherapy followed by high dose busulfan and thiotepa. A prospective assessment of high dose chemotherapy in children with diffuse pontine gliomas. Cancer 2000; 88: 685-92.