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MeSH Terms:

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- Bone Marrow Transplantation
- Child
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- Disease-Free Survival
- Hematopoietic Stem Cell Transplantation*/methods
- Human
- Neoplasms/therapy*
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Autologous stem cell transplantation for solid tumors in children

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The dose-effect relationship in pediatric oncology conventional chemotherapy is emphasized. Rationales for the use of megatherapy protocols with stem cell support and associated procedures are given. It has been more than 15 years since this approach was used in neuroblastoma, and it has subsequently been applied to most of advanced, common childhood solid tumors. The ongoing use of new strategies for dose intensification with peripheral blood stem cell or autologous purged bone marrow rescue has raised expectations for cure. To date, results of megatherapy followed by autologous stem cell reinfusion are encouraging in metastatic neuroblastoma and Ewing's sarcoma, with an increase in event-free survival rates of about 30% as compared with that of conventional treatments. However, with the exception of metastatic neuroblastoma, there is still no proven role for this treatment strategy. Thus, there is still an urgent need for international collaboration to design randomized studies that could rapidly address the issue of these expensive and high-morbidity procedures in childhood cancer.

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Abbreviations

ABMT	autologous bone marrow transplantation
BMT	bone marrow transplantation
CCG	Children's Cancer Group
CR	complete response
EBMTSTR	European Bone Marrow Transplantation Solid Tumour Registry
EFS	event-free survival
PBSC	peripheral blood stem cell
PR	partial response
RFS	relapse-free survival
SCT	stem cell transplantation
SFOP	French Society of Pediatric Oncology
TBI	total body irradiation
VAC	vincristin, actinomycin D, cyclophospamide
VGPR	very good partial response
WHO	World Health Organization

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The demonstration that myeloablative megatherapy supported by stem cell infusions can cure patients with hematologic malignancies resistant to standard treatment has led to the introduction of this therapeutic approach in poor prognosis solid tumors starting in the late 1970s. Approximately 2000 pediatric patients with solid tumors have received myeloablative megatherapy in Europe. However, given the relative rarity of this group of cancer, phase III comparative trials are still awaited. Thus, to date we still have to rely on single-center reports, pilot or single arm studies, or registry data to estimate the impact of myeloablative megatherapy on outcome in children with poor prognosis solid tumors.

In this review we highlight the most recent reports associated with the field of megatherapy followed by stem cell rescue in pediatric oncology. For more detailed information the interested reader is directed to earlier comprehensive reports and review articles cited throughout the text.

Rationale of myeloablative megatherapy for solid tumors

In solid tumors, the principle of a dose effect was readily demonstrated *in vitro* [1], whereas such a close relationship is often less apparent *in vivo*. However, there are some clinical cases, *ie*, in neuroblastoma, Ewing's sarcoma, and rhabdomyosarcoma, in which increased but still nonmyeloablative doses of cyclophosphamide or ifosfamide were associated with increased efficacy [2–5]. Thus concepts of myeloablative, high-dose chemotherapy with or without total body irradiation (TBI) evolved. Ideally, a megatherapy regimen should consist of an agent or agents that are not schedule dependent, are known to have a steep dose-response curve for the particular tumor being treated, and have little if any extramedullary toxicity, particularly nonoverlapping organ toxicities. Otherwise, there is inevitably a need to reduce the dose of one or all of the agents included with the consequent likelihood of reduced efficacy. In addition, long-term sequelae must be considered, including chronic injury to the lung, kidney, liver, heart, or brain as well as endocrine hypofunction.

The bifunctional alkylating agent melphalan was selected as a suitable agent for such a strategy because of its predominantly hematologic dose-limiting toxicity and its short half-life allowing the use of noncryopreserved bone marrow. Melphalan is one of the few drugs that has been demonstrated to have clear activity at high dose in relapsed or refractory childhood solid tumors [6–9]. This

agent still forms the backbone of most megatherapy regimens. Other drugs for which there are limited single-agent phase II data include high-dose etoposide and high-dose thiotepa [10–14]. Several complex regimens have been evolved, including other alkylating agents such as cyclophosphamide or to a lesser degree busulfan, but also carboplatin and doxorubicin; however, to date none have been clearly shown to be better than melphalan alone.

Although conventional-dose irradiation therapy plays an important role in the elimination of residual disease following chemotherapy for many childhood solid tumors, the efficacy of a single high-dose fraction of TBI given in several divided doses is less clear. Early studies with either hemicorporeal irradiation or low-dose hyperfractionated TBI demonstrated some efficacy in resistant tumors such as Ewing's sarcoma [15]. This was often limited to pain relief only. Only one *in vitro* radiobiologic study in neuroblastoma sheds some light on this issue, demonstrating a steep dose-response curve with little, if any, early shoulder, indicating minimal repair at low dose [16]. This was used as evidence for the application of fractionated TBI in this disease.

Source of stem cells

Autologous peripheral blood stem cells (PBSCs) instead of autologous bone marrows are increasingly used even in small children with body weights reported as low as 8 to 10 kg [17,18•,19•,20–22]. This results from the general recognition that neutrophil and platelet recovery after reinfusion is faster than with autologous or allogeneic bone marrow with or without hematopoietic growth factors. The first randomized trial comparing superiority of PBSC over bone marrow autotransplantation in patients treated with megatherapy for solid tumors or lymphomas clearly demonstrated the superiority of PBSC [23••]. Success depends on the optimized mobilization or release of stem cells [24–26]. The threshold dose for rapid hematopoietic reconstitution is about 2×10^6 $CD34^+$ cells/kg body weight. In our experience, 15 to 20×10^6 $CD34^+$ cells/kg can be harvested after one mobilization course with two to three apheresis sessions. This is of particular interest when repetitive courses of megatherapy are considered. In this case, a higher range of 5 to 10×10^6 $CD34^+$ cells/kg could be considered, permitting a quick recovery, including platelets [27•,28] and outpatient care, even of pediatric patients. However, potential reinfusion of mobilized tumor cells has to be considered implicating that the quality of PBSC harvests have to be carefully monitored with help of adequate modern laboratory techniques according to tumor cell type, *ie*, polymerase chain reaction or specific monoclonal antibodies [29,30••,31]. This is a major issue when sampling is performed during the early treatment phase, which has the advantage of a less depleted or disturbed stem cell pool resulting in better harvests of $CD34^+$ cells.

To purge or not to purge?

With the use of polymerase chain reaction techniques there is an increasing number of reports discussing the hazards of tumor cell–contaminated stem cell harvests [32•]. Because some authors describe bone marrow positivity in low-stage disease with excellent prognosis, one must question the usefulness of such results. Thus international standards are urgently required to standardize the methodology and to validate the different techniques and interpretation of data as a prerequisite for its use in clinics. The French LMCE group and the Italian Institute Gaslini retrospectively addressed the purging question [33]. Both groups had comparable initial cisplatin-based chemotherapy regimens and used high-dose megatherapy combining TBI, vincristine, and either melphalan or petichemio. There was no evidence of any difference in outcome between the Italian group, for whom purging was not routinely used, or the French, for whom immunomagnetic purging was routine.

Minimal residual disease still appears as the pertinent problem but recent developments using early repetitive cycles of megatherapy might help to overcome the development of resistant clones. The new interest in purging of stem cell harvest was also kindled through the elegant studies by the group of Rill *et al.* [34] involving labeling of reinfused marrow with *NEO-R* gene. The rationale for their initial protocols was to learn whether residual malignant cells in autologous marrow contribute to subsequent relapse. Marked malignant cells were found at the time of relapse in six of eight patients relapsing after autologous bone marrow transplantation (ABMT) for acute myeloblastic leukemia or neuroblastoma showing the infused marrow contributed to disease recurrence. Because ABMT may return a multiplicity of tumorigenic tumor cells, modifications of this marker approach with two distinguishable vectors are now being used to compare the efficacy of purging techniques [34,35,36••].

In the past, purging of autologous bone marrows with immunomagnetic beads or mafosfamide translated into a delay of hematopoietic recovery of approximately 1 week [37] with all the associated risks of prolonged aplasia. Because PBSC sampling does allow higher stem cell yields, this disadvantage could disappear.

Various purging procedures can be considered. One of them is positive stem cell selection, although its effectiveness in solid tumors must still be questioned because of unsatisfactory log reduction (one to four logs) of contaminating tumor cells and loss of $CD34^+$ cells up to 50% with methods being clinically approved to date. Civin *et al.* [38] reported a pilot feasibility clinical trial involving 13 young patients 25 years of age or younger with advanced solid tumors, including seven children with neuroblastoma whose harvested bone marrow underwent immunomagnetic $CD34^+$ selection. It must be noted that in three of

13 enrolled patients, low purity of the $CD34^+$ preparations disqualified the use of the $CD34^+$ marrow grafts. In the 10 patients transplanted with $CD34^+$-selected cells, the $CD34^+$ cell purity (nucleated erythrocytes excluded) in the cell graft preparation was 91% total cell recovery from the starting light-density cells 2.2%, $CD34^+$ cell recovery 38%, colony-forming unit granulocyte-macrophage recovery 23%, and estimated tumor cell depletion 2.6 logs (median). The $CD34^+$ marrow grafts contained a median 1.4×10^6 $CD34^+$ cells per kilogram patient weight, and all 10 patients engrafted.

Kanold *et al.* [19•] reported the successful $CD34^+$ cell immunoselection from granulocyte colony-stimulating factor alone primed peripheral blood (10 μg/kg/d subcutaneously) in nine children with neuroblastoma with a median body weight of 16 kg (range, 10 to 20 kg). The yield of $CD34^+$ cells in the purified fraction was 50% (range, 23% to 80%), with a median number of 2.8×10^6 $CD34^+$ cells/kg (range, 1 to 9.4×10^6). The megatherapy regimen contained busulphan and melphalan, and all patients had persistent engraftment.

Another approach could be the use of the anti-GD2 antibody [39], which has a direct cytotoxic effect on neuroblastoma cells and may be an effective way of achieving tumor depletion *in vitro* once this antibody becomes commercially available. This technique has also been used in clinical practice [30••].

However, the major issue with purging is not a debate about the feasibility of producing a 2 to 4 log depletion from marrow but rather the relevance of this in clinical practice. Results in neuroblastoma in which allogeneic BMT have been used have failed to show any significant benefit. In contrast, hazards of acute and chronic graft-versus-host disease have adversely influenced outcome in published series [40,41]. However, these studies, if they were to show a benefit, would not distinguish from the potential graft-versus-tumor effect as opposed to absent risk of reinfusing tumor cells. Due to numbers it is impracticable to expect an answer from the more appropriate syngeneic transplant comparison. There is still no randomized study in either solid or hematologic malignancies addressing the issue of purging, and decision to purge or not is based mostly on personal opinion, as well as practical and financial considerations or concern about potential morbidity associated with an adverse effect on the autologous bone marrow engraftment.

Neuroblastoma

At diagnosis, about 65% of affected children show disseminated disease, most frequently involving bone marrow and bones. Historical control groups during the 1970s had a survival expectancy of only 10% at 3 years with conventional multimodality treatments. During the past decade, the use of modern intense induction treatments and intensification with myeloablative megatherapy regimens followed by stem cell transplantation (SCT) have improved the prognosis of stage 4 neuroblastoma over 1 year of age at diagnosis to a range of 40% to 60% at 2 years according to various reports [42–53,54•]. However, patients continue to relapse, and 5-year survival rates of larger series are still in the range of 30% to 40% but leaving even a survivor of 5 years with only an 80% chance for continuous remission [53]. It should be mentioned that upfront dose escalation without PBSC replacement still might strongly influence future overall results. Following earlier reports on intensified use of platinum derivatives and VP16 [55–58], Kushner and Helson [59] had put weight on high doses of cyclophosphamide and continuous infusions of doxorubicin and vincristine. Another recent report by Campbell *et al.* [60] was able to demonstrate that even in patients with neuroblastoma refractory to standard chemotherapy or with progressing disease, impressive response could be produced when cisplatin, etoposide, and doxorubicin were administered as continuous infusions for 96 hours with daily ifosfamide bolus injections. Drugs were escalated at six dose levels. The overall response rate was 43% and even reached 50% to 60% at the fifth and sixth dose escalation levels [60].

A 1993 consensus conference in Lyon reviewed the role of high-dose therapy with stem cell rescue in a variety of malignancies including childhood tumors. Following this symposium, the development of megatherapy strategies in neuroblastoma, details of high-dose megatherapy regimens, as well as the results of the various clinical trials up to 1992 have been extensively discussed [4]. Additional arguments for and against megatherapy were detailed in two further contributions [61,62].

Update on the European experience with megatherapy and stem cell transplantation in stage 4 neuroblastoma

The European Bone Marrow Transplantation Solid Tumour Registry (EBMTSTR) contains detailed, controlled information on children with advanced neuroblastoma who received megatherapy followed by SCT [54•]. Between 1979 and 1996, 1070 neuroblastomas were collected. Median age at diagnosis was 3 years (range, 1 day to 30 years) and the median observation time was 16 months (range, 1 day to 168 months). A total of 905 patients were consolidated in first complete response (CR) or first partial response (PR), and 129 were relapses or progressions (36 unknown). With a median follow-up of 75 months, a 33% overall survival is observed at 5 years. Of the patients, 49% are alive after 2 years and 10% of the relapses are observed between 24 and 48 months after stem cell reinfusion. Twenty percent of the patients are still at risk of relapses after 48 months. Among the 905 patients with consolidation as first-line treatment, no difference is found between CR and PR and between

very good partial response (VGPR) and CR at the time of BMT. Patients receiving a single-graft program (746 patients) are doing as well as those receiving double-graft programs (159 patients). Patients receiving regimens containing TBI (346 patients) are doing as well but not better than those receiving regimens using only high-dose chemotherapy (559 patients). The toxic death rate is 12.4% for first CR, 14% for PR and VGPR, and 14% for relapses. However, the group of 346 patients receiving TBI experienced significantly more toxic deaths (18%) than the group treated by megatherapy not containing TBI (11%); ($P < 0.005$). Single- and double-graft programs had equivalent toxic death rates.

These 17 years of European experience gathered in the EBMTSTR database have been used to analyze reasonable subsets of this patient cohort to shed some light on indications and prognostic factors and their relationship with outcome. Potential prognostic factors to predict event-free survival (EFS) were investigated in 546 patients fulfilling the inclusion criteria for analysis, *ie*, stage 4 neuroblastoma, age over 1 year at diagnosis, and no relapse prior to the megatherapy. Their response status prior to megatherapy was as follows: first CR in 157 patients, first VGPR in 156, PR in 208, and minor response in 24. Of 546 patients, 110 received a twin megatherapy procedure. The EFS was 26% at 5 years. Multivariate analysis by the Cox proportional hazards regression model included 529 patients with complete data sets. Two adverse, independent risk factors influencing EFS were identified after adjustment to treatment duration prior to megatherapy and twin megatherapy procedures. Persisting skeletal lesions prior to megatherapy defined by ^{99}Tc scans or mIBG (metaiodobenzylguanidine) scans appeared as the major risk factor in predicting outcome ($P = 0.0018$) and persisting bone marrow involvement prior to megatherapy ($P = 0.0237$). Thus, residual skeletal disease after induction treatment as defined by mIBG scans in children with stage 4 neuroblastoma could be an additional tool to decide on further treatment intensity [63].

Patients who received megatherapy and SCT after relapse (129 patients) show an overall 5-year survival rate of 24%. Second or subsequent relapse after initial stage 4 disease was the indication for megatherapy in 48 patients at the time the analysis was performed. When megatherapy had been previously used as consolidation of first CR, no salvage was possible, whereas 15% of patients may survive when megatherapy is used for the first time at relapse. It was suggested that only responding patients who relapse more than 12 months from diagnosis without a previous megatherapy could benefit from megatherapy at the time of relapse [64].

A further critical analysis concerned infants with stage 4 neuroblastoma. In view of actuarial survival rates of up to 75% with conventional dose chemotherapy and surgery, toxicity hazards of megatherapy should be avoided in infants with good response, especially when favorable biology according to recent standards is documented. The 5-year overall survival was only 55% in 18 infants with stage 4 disease recorded in the registry and was 77% for infants in CR or VGPR prior to megatherapy. The toxic death rate was as high as 17%. Thus the role of early megatherapy in infants should be limited to desperate cases with persistent, biopsy-proven metastases after conventional dose chemotherapy or nonresponding patients [65].

A matched-pair analysis was performed in advanced or poorly responding, first remission neuroblastoma cases to investigate a potential graft-versus-tumor effect resulting from allogeneic BMT (17 patients) [66]. Pairs were matched on the bases of prognostic factors including age, gender, prior treatment durations, pregraft response status, and bone and bone marrow involvement before BMT, including only patients with only one BMT. No difference in progression-free survival rates were detected comparing the outcome after 17 allogeneic and 34 autologous BMTs: 35% and 41% at 2 years, respectively. Graft-versus-host disease was observed in nine of 17 patients (grade I or II in seven and grade IV in two). This analysis concluded that ABMT appears to be at least equal to allogeneic BMT.

The same question was addressed by the Children's Cancer Group (CCG) in two protocols using myeloablative megatherapy with allogeneic or autologous purged bone marrow rescue for high-risk patients with neuroblastoma who were progression free at the end of induction chemotherapy. Allogeneic BMT did not have a better outcome than ABMT [41].

A review by the International Bone Marrow Transplant Registry also reported a similar relapse rate with use of allogenic BMT as compared with ABMT. At 17 months, there were 29 patients of 92 with continuous complete remission [39,40]. These results do not favor allogeneic BMT in neuroblastoma, especially considering the associated toxicity hazards, many of which are related to prior cisplatin therapy and renal dysfunction [67].

Recent reports of major groups

Controversial issues were recently highlighted in an editorial of Kamani [68] on the bases of results of major American study groups including the Pediatric Oncology Group, the CCG, the Children's Hospital of Philadelphia, and American Bone Marrow Transplantation Registry data. Issues still regarded as unsolved are the role of megatherapy with SCT over intensive chemotherapy without SCT, the type of graft, and the role of *in vitro* treatment of the graft as well as optimal timing of the transplantation.

These groups recently reported results of ABMT for advanced neuroblastoma using all total body irradiation-containing regimens: The CCG group compared two studies to determine EFS for 207 patients with stage IV neuroblastoma after 1 year of age who were treated with induction chemotherapy followed either by additional courses of the same chemotherapy (74 patients) or by megatherapy (VAMP with TBI; PEM with TBI; or CEM with TBI) and ABMT (67 patients). The treatment decision was elective and not randomized. Marrows were purged *ex vivo* and were free of immunocytologically detectable neuroblastoma cells. EFS estimates at 4 years were in favor of the megatherapy arm, with 40% in the chemotherapy group versus 19% in the megatherapy plus ABMT group, respectively ($P = 0.019$). Two subgroups especially were shown to benefit from the intensified treatment approach: patients with PR only after induction treatment (EFS, 29% vs 6%; $P = 0.008$) and those whose tumors had amplification of the N-*myc* gene (EFS, 67% vs 0%; $P = 0.1$). Thus, this retrospective comparison suggested superiority of intensive, myeloablative chemoradiotherapy and purged ABMT over continued conventional-dose chemotherapy [69•,70]. A randomized, prospective trial comparing myeloablative therapy with ABMT to continuous infusion consolidation chemotherapy by the CCG is currently underway to determine the relative benefit.

In 1994, Evans *et al.* [67] updated the results from the initial Philadelphia series including 42 patients. Twenty-five of 27 relapsed patients had originally stage IV, and 15 entered as part of their initial treatments (12 stage IV and three stage III). Treatment was based on debulking with aggressive surgery and local radiation therapy followed by megatherapy with TBI. Twelve of 43 patients had matched sibling donors and thus underwent allogeneic BMT. The majority of autologous bone marrows were purged. The 4-year actuarial survival rate was 29%. Ten patients died of early treatment-related complications within 3 months, 18 of progressive disease, and two of late complications (one AIDS and one acute myelogenous leukemia). Survival rate after ABMT was 30% and only 7% in the allogeneic group (not statistically different).

Graham-Pole on behalf of the Pediatric Oncology Group has reported on a series of 74 children with metastatic neuroblastoma who were autografted following a combination of melphalan (60 mg/m^2) three times and TBI (1.5 or 2 Gy) in six fractions [40]. Immunomagnetic purging of the bone marrow was done on 64 patients. Fifty-four patients were treated in first CR or PR and the 2-year EFS was 32% and 43%, respectively. Relapse patients had EFS rates of 33% and 5% for those in second CR and second PR, respectively. A third of patients also received local irradiation to sites of persisting disease following high-dose therapy. There was a significantly better outcome for patients given a higher TBI dose, *ie*, 12 Gy. It also appeared that patients given local irradiation following transplantation did significantly better than those who did not. It should be emphasized that this and the TBI dose were not randomly assigned and that the numbers were comparatively small.

The Genova group described 34 cases treated with a similar high-dose regimen to that used by the LMCE group [49]. Multiagent regimens adding high-dose carboplatin and etoposide have been disappointing, with increased morbidity and no fewer relapses than after melphalan alone [45,46]. Morbidity of the above regimens and the respective progression-free survival at 2 years were previously summarized [4]. Comparing results produced by aggressive regimens including TBI and local radiation in comparison with results of European groups not using TBI [54•], it must be stated that success rates are approximately the same.

The Australian group used a strategy aiming to achieve remission with an induction combination of intensive chemotherapy, primary resection, and tumor-bed radiotherapy [52]. Patients who achieved remission proceeded to myeloablative chemoradiotherapy using a modified VAMP with TBI regimen (teniposide 130 mg/m^2, doxorubicin 30 mg/m^2, melphalan 120 mg/m^2, cisplatin 80 mg/m^2, and TBI 12 Gy in six fractions) and unpurged ABMT. Seventeen of 28 patients older than 1 year presented with stage IV disease during the study period and proceeded to ABMT. Survival rates of all 28 patients are 61% and 50% at 2 and 5 years, respectively. Fifteen of 17 patients after megatherapy remained disease free, with no toxic deaths. This result compares favorably with that of other groups, but larger numbers of patients must be treated to confirm the efficacy of this therapy. Two reports investigated recently the pattern of relapse after megatherapy with ABMT.

The CCG group [70] analyzed the relapse pattern in 41 of 99 patients who had undergone ABMT after induction chemotherapy, surgery with or without local radiation, and then myeloablative therapy with teniposide (or etoposide), melphalan, doxorubicin, cisplatin, and TBI. The overall probability of relapse 36 months after ABMT was 49%. Both bone and bone marrow involvement at diagnosis correlated with specific relapse in that site ($P < 0.05$). Bone marrow tumor content at harvest greater than 0.1% also correlated with bone marrow relapse ($P = 0.001$). There was an association between incomplete resection of the primary tumor at diagnosis and relapse in that site ($P = 0.06$).

The role of a local radiotherapy boost of 8 to 24 Gy given to the primary or metastatic sites was also emphasized by Sibley *et al.* [71•] for children with advanced or relapsed neuroblastoma. The actuarial overall survival of the 26 patients was 40.4% at 3 and 5 years undergoing megather-

apy with TBI (4 × 50 mg/kg cyclophosphamide and 12 Gy TBI) and ABMT. Sites not amenable to a radiotherapy boost included the bone marrow, diffuse or bilateral lung involvement, and multiple bone metastases (more than four sites). Overall, this study demonstrated a trend toward less failure in sites amenable to a radiotherapy boost and thus better local control of these. It should be noted that disease recurrence following BMT was most common in previous sites of disease. Thus, these reports highlighted that neuroblastoma normally recurs in multiple sites after ABMT, particularly in areas of previous disease and suggest that neuroblastoma cells in the graft are still not the major cause of relapse. More intensive treatment to known areas of disease (aggressive early surgery, effective myeloablative consolidation therapy) and after ABMT therapy for minimal residual disease should thus be studied for their potential to decrease the frequency of relapse. Most relapses after megatherapy with ABMT still occur at sites of bulk disease or previously involved sites in spite of aggressive local treatment.

Complementary treatments after megatherapy and autologous bone marrow transplantation

Additional complementary treatment after megatherapy with SCT began to interest various groups because some treatment approaches appear to have an interesting potential to overcome minimal residual disease. The rationale to use interleukin-2 to enhance the immune response against the tumor and thereby to improve survival of these patients has attracted various groups. So far groups reporting interleukin-2 results after autograft used high-dose intravenous interleukin-2 within a range of 12 to 18 × 10^6 IU/m^2 [72–75]. Although the French group did not see impressive results with this application mode a recent report is more enthusiastic [76•]. However, the use of high intravenous doses has produced grade 3 to 4 World Health Organization (WHO) organ toxicities. When used after megatherapy with ABMT, only limited numbers of patients were able to receive recombinant interleukin-2 therapy due to delay in platelet recovery. However, with the use of higher stem cell doses as currently available by PBSC harvests, this problem might be overcome. Earlier administration of low-dose recombinant interleukin-2 after megatherapy with SCT, given subcutaneously and combined with an *ex vivo* recombinant interleukin-2 treatment of the graft could be a more valid way of using recombinant interleukin-2 to improve survival.

Another promising approach for the situation of minimal residual disease after megatherapy with SCT appears to be the use of an chimeric antibody anti-GD2 [30••]. A phase I study of human and mouse chimeric antiganglioside GD2 antibody ch14.18 was performed in nine patients with neuroblastoma with stage IV neuroblastoma receiving a total of 19 courses of the anti-GD2 antibody ch14.18 at dose levels of 30, 40, and 50 mg/m^2/d for 5 days per course. The maximum tolerated dose per injection was 50 mg/m^2/d. Clinical side effects of patients treated with ch14.18 were abdominal and joint pains, pruritus, and urticaria. A complete remission was seen in two patients, partial remission in two patients, minor response in one patient, and stable disease in one patient. These results indicate that treatment with chimeric monoclonal antibody ch14.18 can elicit some complete and partial tumor responses in patients with neuroblastoma.

Because treatment of neuroblastoma cell lines with cis-RA (13-cis-retinoic acid) can cause sustained inhibition of proliferation and cis-RA has demonstrated clinical responses in patients with neuroblastoma, it was considered that it may be effective in preventing relapse after cytotoxic therapy [77•]. In a phase I trial, maximum tolerated dosage, toxicities, and pharmacokinetics of cis-RA administered on an intermittent schedule were determined in 51 children with neuroblastoma following megatherapy with BMT. Oral cis-RA was administered in two equally divided doses daily for 2 weeks, followed by a 2-week rest period, for up to 12 courses with doses escalated from 100 to 200 mg/m^2/d. The maximum tolerated dose of cis-RA was 160 mg/m^2/d. Dose-limiting toxicities in six of nine patients at 200 mg/m^2/d included hypercalcemia, rash, anemia with thrombocytopenia, and emesis. All toxicities resolved after cis-RA was discontinued. Serum levels known to be effective against neuroblastoma *in vitro* were achieved at this dose. The dose-limiting toxicity included hypercalcemia and may be predicted by serum cis-RA levels. Interestingly, three complete responses were observed in marrow metastases, and thus cis-RA merits further investigation in this setting.

One recent report from a Japanese group describes such a strategy involving intensive induction chemotherapy, surgery, intraoperative radiation, megatherapy and purged ABMT followed by cis retinoid acid. This strategy offered a 3-year disease-free survival rate of 72% to the 22 children treated for advanced neuroblastoma. However, no conclusions can be made regarding the role of the different modalities used in this pilot study [78].

Biology

In the future, biologic factors might contribute to define highly aggressive disease more accurately. N-*myc* amplified tumors clearly are associated with an inferior prognosis in localized disease [79–83], but only a few authors have described the same prognostic value in stage 4 disease [79]. For deletions of the short arm of chromosome 1 (del 1p) the prognostic value is even less clear, although preliminary data exists [84,85••,86]. First reports suggest that it could play a role also for stage 4 disease [79]. The same is true for CD44 expression molecules, which were described to isolate a better prognosis subgroup also in stage 4 disease [87,88••]. For both of the

latter two factors confirmation has to be awaited. Serologic prognostic factors, however, *ie*, lactic dehydrogenase, ferritin, and neuron-specific enolase, identify well the patient with stage 4 disease [86,89,90] but have rarely been demonstrated to distinguish prognostic subgroups within this group [90,91]. Thus, biologic characteristics will increasingly contribute to decisions for megatherapy concepts in the future, especially when patients who respond poorly or those with bulky disease, even if not disseminated, are concerned.

Rhabdomyosarcoma

Long-term survival now exceeds 70% in European and American series [92,93]. This rate is achieved with combination of chemotherapy using vincristine, actinomycin, and ifosfamide or cyclophosphamide. There remain, however, some high-risk groups, such as those presenting with initial metastatic disease, in whom the cure rate rarely exceeds 20%, and those with parameningeal disease or those in whom complete remission is not achievable with chemotherapy combined with surgery. In these patients, dose escalation is worthy of investigation. Phase II studies with single agents at high doses are rare. As with neuroblastoma, the exception is the use of high-dose melphalan, and small phase II studies have demonstrated response rates of 40% to 50% [8,94]. Anecdotal series have described CR and PR using combinations of high-dose busulphan and cyclophosphamide, melphalan with TBI, cyclophosphamide-dacarbazine-doxorubicin, and high-dose carmustine [32•,43,95,96]. Because of the small numbers involved, few conclusions can be drawn from these results. Indications for megatherapy in rhabdomyosarcoma are as consolidation of initial CR or PR in high-risk disease or of second CR after relapse. Cure rate following relapse is largely dependent on the intensity of the first-line chemotherapy and whether radiotherapy was given. If radiotherapy has not been used or a limited number of agents have been given initially, *ie*, for initially completely resected disease, then a cure rate of around 50% is achievable with second-line chemotherapy, surgery, and radiotherapy in the absence of megatherapy [97]. If, however, initial treatment has been more intensive, then dose escalation is warranted provided that a response is achieved with second-line chemotherapy. As in the case of neuroblastoma, until there is evidence of a higher response rate in phase II studies using new agents at high dose or combinations of chemotherapy, high-dose melphalan remains the agent of choice. A clear dose effect has been demonstrated for melphalan in the rhabdomyosarcoma xenograft model [98], and at a low dose this agent is also active in relapsed or refractory disease [99].

A series of 43 children with rhabdomyosarcoma treated at the Royal Marsden Hospital over a 10-year period using the rapid vincristin, actinomycin D, cyclophosphamide (VAC) regimen over an 8-week period followed by high-dose melphalan and nonpurged autograft showed 3-year relapse-free survival for those with stage 3 and 4 disease of 55% and 25%, respectively. This strategy of very short high-dose intensity treatment, despite initial short-term morbidity, is probably as safe in the short and long term as more prolonged chemotherapy or the intensive pulsed regimen such as IVA (ifosfamide, vincristin, actinomycin) [100]. The impact of megatherapy for patients with initial metastatic disease is unclear, and in the Royal Marsden Hospital series the 25% survival was little different to that reported by the Intergroup Rhabdomyosarcoma Study or European groups using more prolonged conventional chemotherapy [92,101].

A recent paper described the results of a multicenter, retrospective analysis of 36 patients with primary metastatic disease ($n = 27$) or relapsed rhabdomyosarcoma ($n = 9$) treated between 1986 and 1994 according to the German Soft Tissue Sarcoma Studies or in the European Study for Stage IV Malignant Mesenchymal Tumors in Childhood. There were 22 alveolar rhabdomyosarcoma, 13 embryonal rhabdomyosarcoma, and one undifferentiated sarcoma. Thirty-two patients were in first or second CR and four had a good PR. Megatherapy consisted of melphalan, etoposide and carboplatin in 26 patients, 10 of whom received additional TBI. The others had various regimens, including melphalan in seven patients. Nine of 36 patients are alive and free of disease with a median observation time of 57 months. The median time from high-dose chemotherapy to relapse was 4 months, and the tumor recurred in the majority of patients at previously known sites. Patients with primary localized tumors who had been treated with megatherapy because of relapse did slightly better (four of nine alive with no evidence of disease) than patients with primary metastic disease (five of 27 alive with no evidence of disease) [102].

The International Society of Pediatric Oncology MMT 90 metastatic study has added high-dose melphalan (200 mg/m^2) with unpurged BMT to an intensive multiagent regimen. The latter has been previously used on 52 patients in whom, despite an encouraging CR rate with chemotherapy alone, the relapse-free survival has been disappointing. It is hoped that consolidation of CR will improve this.

The 1996 analysis of the EBMTSTR found 319 patient grafted for soft tissue sarcomas. A total of 233 of 319 patients with rhabdomyosarcoma who received megatherapy had an overall 5-year survival rate of 21%. The 5-year survival rates were 31% for 90 patients grafted in first CR and 26% for 138 patients consolidated during first treatment intention but only 12% in 90 patients treated at the time of relapse or disease progression. The high-dose regimens used included melphalan, melphalan with TBI, carmustine with melphalan, and procarbazine-melphalan-

etoposide [103]. Interpretation of these data still are difficult because of the heterogeneous nature of the patients, the different initial chemotherapy protocols, and the range of megatherapy regimens.

Ewing's sarcoma

Dose intensification using ifosfamide, vincristine, and doxorubicin in the United Kingdom Ewing's Tumor 2 trial or in the German Cooperative Ewing's Sarcoma Study series with additional etoposide has increased the relapse-free survival to around 70% at 3 years [3]. A very high-dose but short-term chemotherapy schedule using high-dose CAV (cyclophosphamide, doxorubicin, and vincristine) was investigated by the Memorial Sloan Kettering Group in poor-risk peripheral primitive neuroectodermal tumors [104], *ie*, because of a tumor volume more than 100 cm^3 or metastases to bone or bone marrow. The P6 protocol consists of four courses (1, 2, 3, and 6) high-dose CAV (cyclophosphamide 4,2 g/m^2 per course plus 72-hour infusions of doxorubicin 75 mg/m^2 and vincristine 2.0 mg) and three courses 4, 5, and 7 ifosfamide 1.8 g/m2/d and etoposide 100 $mg/m^2/d$, for 5 days. The authors reported an excellent antitumor efficacy (excellent histopathologic or clinical responses in 34 patients and PRs in two patients). For 24 patients with locoregional disease, the 2-year EFS rate was 77%. Patient numbers are still small in the Memorial Sloan Kettering Group cohort, but the efficacy of this schedule was also demonstrated by the Vienna group in another series of 18 children and adolescents with poor prognosis recurrent or refractory solid tumors [105]. All enrolled patients were heavily pretreated, including two patients after BMT. Forty courses were applied (median, two). The overall response rate was 33% (two complete remissions and four partial remissions). Responses were obtained in children with neuroblastoma, Ewing's tumors, and hepatocellular carcinoma. Myelosuppression (WHO grade IV after all courses) and cardiac toxicity (three WHO grade I, five WHO grade III, and three WHO grade IV) were the main side effects. Ten of 18 patients were alive after a median follow-up of 16 months but received additional treatments consisting of surgery, radiotherapy, cycles of high-dose platinum derivates and etoposide as well as MEC megatherapy (MEC regimen: mephalan, etoposide, carboplatinum) followed by SCT.

In spite of intensified induction strategies, subgroups remain in whom the outcome still is less favorable, including those with initial distant disease, in particular those with bone marrow or bone metastases. Also those with very bulky initial tumors, often of axial origin, such as the pelvis, but also relapsing patients. In these patients long-term survival rates remain in the region of 20% to 30%. For these groups, investigation of megatherapy procedures is underway and warranted. These risk groups are in line with a recent analysis emerging from the combined data sites of 975 patients coming from the GPOH/European Intergroup Cooperative Ewing's Sarcoma Study and the UK Children's Cancer Study Group/Medical Research Council studies [106•].The key prognostic factor was the presence of metastases at diagnosis (5-year relapse-free survival, 25.3% vs 55.2%; $P < 0.0001$). However, patients with lung metastases only had a better survival in comparison with patients with other metastatic sites. The rather favorable outlook of patients with only pulmonary metastases had been reported previously by the GPOH/Cooperative Ewing's Sarcoma Study studies [107•]. In the group of patients without primary metastases, the following significant adverse risk factors were isolated: axial primaries (RFS, 49.6% vs 61.4%), age over 15 years (RFS, 48.8% vs 59.9%), treatment period before 1985 (RFS, 45.5% vs 60%) and time to relapse within 2 years after diagnosis (RFS, 3.9% vs 23.3%).

Again, the only single agent that has been adequately evaluated is high-dose melphalan, and a review of response rates by Hartmann *et al.* [7] showed 11 complete responses in 27 patients. Combination regimens such as busulphan, cyclophosphamide, or TBI-based regimens have been reported as effective [94]. Another report from the Institute Gustave Roussy [108] emerged analyzing the experience on 32 children treated for metastatic Ewing's sarcoma by megatherapy and ABMT. Of special interest were 14 patients who entered phase II studies of high-dose alkylating agents displaying a response rate of 61%.

Another series comes from the National Cancer Institute where patients with Ewing's sarcoma of the central axis or any site with metastases ($n = 66$) or with high-risk rhabdomyosarcoma ($n = 25$) received initial VAC chemotherapy followed by 8 Gy TBI with ABMT and further VAC. Only 65 to 91 received consolidation therapy, and 20 became long-term event-free survivors. Patients with metastatic disease at diagnosis fared substantially worse than did patients with localized tumors (6-year EFS rate, 14% vs 38%; $P = 0.008$). This study demonstrated that consolidation of patients with metastatic or high-risk localized pediatric sarcomas with 8 Gy TBI plus ABMT failed to improve the outcome of the studied patients [109].

In a cooperative study between Vienna and Düsseldorf Children's Hospital Medical Centers (Austria and Germany) the efficacy and feasibility of the ME (± C) regimen [1] given as consolidation treatment to seven patients with multifocal primary and 10 patients with early or multiple relapsing Ewing's sarcoma was evaluated. Megatherapy consisted of 12 Gy TBI plus fractionated melphalan (30 to 45 mg/m^2 for 4 days) followed by high-dose etoposide (40 to 60 mg/kg) with or without carboplatin (900 to 1500 mg/m^2) (hyper-ME ± C) [110]. A matched-cohort analysis of the 17 grafted patients with 41 historic controls matched for gender, age, diagnosis, extent of disease, interval from diagnosis to transplanta-

tion in the transplantation group, and interval from diagnosis to relapse in the control group was undertaken. Eight of 17 patients who received megatherapy were alive in complete remission at the median observation time of 49 months (range, 19 to 76 months) from the final event before transplantation. Probability of RFS in the study patients is 45% ± 12% at 6 years since the final event before transplantation as compared with 2% ± 2% for the historic control group. Although a selection process must be considered in all centers receiving referred patients, this study suggests that megatherapy with SCT can prolong survival in multifocal primary and early or multiple relapsing Ewing's sarcoma.

The French Society of Pediatric Oncology (SFOP) reported interesting results in patients with metastatic Ewing's sarcoma treated with megatherapy based on busulphan (600 mg/m^2) and melphalan (140 mg/m^2) at the 28th meeting of the International Society of Pediatric Oncology in 1996. Patients with metastases (n = 44; 23 with isolated lung metastases, six with bone metastases, and 15 with combined metastases) entered the SFOP-EW 91 study. A rather moderate dose induction chemotherapy was used (five VAC courses and two courses with ifosfamide and etoposide) in comparison with that used in other investigations. Although nine of 44 patients progressed under initial treatment, 22 and 12 patients achieved CR and VGPR, respectively. 20 patients are alive in continuous complete remission at a median follow-up of 30 months. The 3-year disease-free survival was 41% for the whole cohort and was 52% for the selected group of 34 patients that underwent megatherapy. This experience compared very favorably with the groups previous experience in the SFOP EW 88 study when semicontinous, conventional dose chemotherapy was used resulting in a 3-year disease-free survival rate of only 12% in a comparable group of patients [111].

The same combination of high-dose melphalan and busulphan is also under evaluation in high-risk patients with Ewing's sarcoma in CR1 at the Royal Marsden Hospital. Of 13 patients with high-risk disease treated following initial chemotherapy with doxorubicin and ifosfamide/etoposide, all but two are in continued remission with a median follow-up of 24 months. There has been one toxic death, but follow-up is still too short to draw conclusions [112].

Further recent experience with 33 patients with high-risk Ewing's sarcoma defined either by primary metastatic disease or pelvic mass was reported by the Italian Association for Pediatric Hematology–Oncology study group at the 28th International Society of Pediatric Oncology meeting [113]. A modified P6 schema was used, *ie*, two cycles of hyper-VAC followed by surgery, radiotherapy, two cycles of standard VAC, and two cycles of ifosfamide and etoposide. The megatherapy regimen consisted of busulphan (16 mg/m^2), etoposide (1800 to 2400 mg/m^2), and thiotepa (300 mg/m^2) followed by peripheral SCT. After a median follow-up of 16 months, 21 patients were alive with no evidence of disease, one was alive with disease, eight patients relapsed (five died), and three more patients with progressing disease died. The event-free survival was 41%. This regimen appeared feasible, but longer follow-up is needed to judge the long-term efficacy of this treatment.

A report from the EBMTSTR analyzed the impact of megatherapy in 63 children with high-risk Ewing's tumors (50 Ewing's sarcomas and 13 peripheral neuroectodermal tumors). The median age at megatherapy was 12 years (range, 1 to 30 years) [114•]. Thirty-two patients with metastatic disease at diagnosis (22 had metastases to the bone or bone marrow) and consolidated in first CR reached an actuarial EFS of 21% at 5 years. Thirty-one patients in second CR achieved an actuarial EFS of 32% at 5 years. Favorable outcome was limited to relapse patients with localized disease at initial diagnosis. Distant relapse had a more favorable prognosis than local failure. Analysis of the different megatherapy strategies could not identify a significantly superior approach, nor is there convincing evidence in favor of double graft procedures. From these results, it appears that consolidation treatment by megatherapy contributes to improved EFS rates in high-risk patients as compared with historical experience. Major questions for the future to be addressed prior to randomized studies include agreement on the definition of high-risk patients and the most efficient megatherapy procedure.

To date, the EBMTSTR holds information on 411 patients with Ewing's tumor transplanted all over Europe. Of 411 patients, 210 were not considered to be in complete remission. Of these 210, 116 were in so-called PR, whereas no or minor response was recorded in 41 patients. Interestingly, the overall response rate in these patients was 53%, with a CR rate of 27%. When relating outcome with response status prior to megatherapy, the overall survival rates were 45% and 19%, respectively. This showed that survival could be equally prolonged in sufficient numbers of patients to consider megatherapy with SCT in patients with residual disease worthwhile unless a patient has progressing disease or resistant relapse. However, no significant difference in survival related to a particular regimen could be detected.

Minimal disease in Ewing's tumors

Minimal primary disease dissemination as well as minimal residual disease are under intensive investigation in Ewing's tumors. The Ewing's family of tumors is characterized at the cytogenetic level by unique chromosome 22 rearrangements. The breakpoints have been cloned and were shown to fuse the *EWS* gene on chromosome 22 to one of two closely related *ETS* proto-oncogenes, *FLI-1* or

ERG, which reside on chromosomes 11 and 21, respectively. The rearrangement results in the expression of chimeric transcripts, which can be identified by means of reverse transcriptase–polymerase chain reaction. This method enables the monitoring of Ewing's tumor cells circulating in the peripheral blood or infiltrating the bone marrow. The presence of tumor cells could be detected with a sensitivity of one in 1×10^6 nucleated cells. However, the clinical implications to date for the presence of Ewing's tumor cells in samples detected by reverse transcriptase–polymerase chain reaction at diagnosis and during therapy are not clear and require further evaluation [115,116•,117•]. Such studies were the background to develop novel techniques to perform *ex vivo* bone marrow or stem cell purging in high-risk Ewing's tumors. A promising new approach was recently described using electroporation to improve intracellular delivery of synthetic antisense oligodeoxynucleotides, thereby enhancing their ability to suppress a target protein. Antisense oligodeoxynucleotides that were introduced into cells by electroporation led to immediate suppression of targeted c-myc protein, which was associated with rapid cell death in various cell lines, including Ewing's sarcoma [118•].

Brain tumors

Tumors in the central nervous system are the most common solid tumors in childhood. Despite undoubted chemosensitivity, there is little evidence that adjuvant chemotherapy following surgery and radiotherapy has had a significant impact on cure, with the exception of certain subgroups of medulloblastoma. Patients with brain tumors are a particularly difficult group to administer megatherapy to at the onset of treatment. The child is often significantly neurologically impaired, and there may be raised intracranial pressure, which is worsened by the hyperhydration necessary for administration of some regimens. Anesthesia for insertion of Hickman line may be undesirable and assessment of response may be difficult.

One of the first drugs studied with ABMT in brain tumors was high dose carmustine. High-dose carmustine given either alone or combined with teniposide and procarbazine produced encouraging responses in adults and children, but the impact on survival was marginal [119,120]. High-dose etoposide has also been used, although mucositis and enterotoxicity limit the usefulness of this agent [121]. EBMTSTR data still show a generally poor outcome for both adults and children using current megatherapy regimens [122]. The rationale, results, and future prospects of megatherapy for brain tumors have been recently reviewed by Wolff [123], whose review can be recommended to the interested reader.

The alkylating agent thiotepa has regained popularity because of its ability to penetrate the blood-brain barrier. It has been used either alone or in combination with etoposide and responses have been seen [11]. A recent study of the CCG group was designed to determine the toxicity, radiographic response rate, and outcome following megatherapy with high-dose thiotepa (3×300 mg/m^2) and etoposide (3×500 mg/m^2) and ABMT for young patients with recurrent brain tumors [124•]. Patients (n = 45) with recurrent high-grade brain tumors (11 glioblastoma multiforme, six anaplastic astrocytoma, one anaplastic ependymo-astrocytoma, three brain stem tumors, three brain stem glioma, one primitive neuroectodermal tumor, nine medulloblastoma, five ependymomas, one choroid plexus carcinoma, two nongerminomatous germ cell tumor, two pineoblastoma, one melanoma) aged 8 months to 36 years (median, 8 years) were treated. The overall response rate in 35 patients with measurable disease and surviving at least 28 days was 23% (two CR, six PR) and was thus not too convincing. The overall survival at 1 year and 2 years was 33% and 16%, respectively. However, survival was reported to be significantly improved in patients with minimal residual disease, but only five patients with high-grade gliomas are alive and disease free 39 to 59 months after megatherapy. The toxic death rate in this series was 16%. The group concluded that thiotepa and etoposide has activity in a variety of recurrent childhood brain tumors and thus merits further evaluation.

Another report stressed the unsatisfactory response of ependymomas to megatherapy containing thiotepa. Between 1988 and 1995, 16 children with relapsed ependymomas entered a phase II study of the SFOP using busulphan (4×150 mg/m^2) and thiotepa (3×300 mg/m^2) followed by ABMT. Fifteen of 16 children were assessed for response. No tumor regression was observed in 50% or more of children. Eleven had stable disease and four progressive disease. Six children who could receive additional radiotherapy or surgery after ABMT were alive in CR 7 to 27 months after ABMT. Extrahematologic toxicity was severe, including mucositis grade III, diarrhea grade III, and veno-occlusive disease.

It appears that treatment of recurrent medulloblastoma in children with megatherapy is more rewarding. Given the severe late effects caused by craniospinal irradiation in children under 3 years of age, most pediatric oncologists are currently treating these patients with conventional chemotherapy in order to postpone or even avoid irradiation. The SFOP investigated the potential of megatherapy with ABMT [125•], aiming to supplant craniospinal irradiation in young children treated for medulloblastoma. Among patients treated without radiotherapy, 20 relapsed while on conventional chemotherapy and were entered in a study of megatherapy and ABMT. Their median age at diagnosis was 23 months (range, 5 to 71 months), and the relapse occurred at a median time of 6.3 months after the initiation of chemotherapy. Four of 20 patients had complete surgical removal of the local relapse, and 16 of 20 had measurable disease at the primary site (nine patients), or at metastatic sites (three patients), or both

(four patients). The conditioning regimen consisted of combination busulphan 600 mg/m^2 over 4 days and thiotepa 900 mg/m^2 over 3 days. After recovery from aplasia, patients with a local relapse received local radiotherapy limited to posterior fossa. Among the 16 patients with measurable disease, a response rate of 75% was observed (six CR, six PR, three no response) following megatherapy (response rate, 75%). For the 20 patients, the EFS is 50% at the median follow up of 31 months after BMT. Ten patients who developed a local relapse or local progression are alive with no evidence of disease without craniospinal irradiation. Among the seven patients who developed metastases or progression of metastases, only one is alive. Toxicity was high but manageable: higher than grade 2 mucositis and diarrhea were observed in 60% of patients. One complication-related death occurred 1 month after BMT. Megatherapy proved to be very efficient in relapsed medulloblastoma but longer follow-up is still necessary to demonstrate whether megatherapy could replace craniospinal irradiation after a local relapse.

Wilms' tumor

The majority of children with Wilms' tumor are cured by chemotherapy. There is no place for high morbidity regimens in the initial management of favorable histology Wilms' tumor of any stage. Only in the unfavorable rhabdoid histologic subtype, for which cure rates are still less than 30% for patients with nonlocalized disease, intensive chemotherapy might be considered. Even following relapse some patients can be salvaged, although this may be fewer than previously assumed [126]. Although patients with localized disease who receive minimal chemotherapy may be salvaged using multiagent regimens, few patients with initial stage III or IV disease can be cured with conventional salvage protocols. It is in this subgroup that interesting data are emerging, and there may be a definite role for megatherapy. Theoretically, the highly chemosensitive Wilms' tumor may resemble B cell non-Hodgkin's lymphoma, which remains curable after relapse by dose escalation of drugs used during initial treatment. A small number of children included in early phase II studies with high-dose melphalan showed activity in refractory patients [93].

A review of the EBMTSTR experience with this tumor reported on 25 children who were treated with megatherapy [127]. At diagnosis, 12 had presented with metastatic disease, whereas 13 had local disease (stage I to III). However, 21 of 25 had experienced one to four relapses. Prior to megatherapy, 17 children were in CR and eight had mesurable disease. Most megatherapy included melphalan and vincristine. Of the 17 patients grafted in CR, eight were alive and disease free at 14 to 90 months. Of eight patients with measurable disease at megatherapy, five achieved CR, but only one of eight was still alive. Overall, the EFS for the 25 patients was 34% at a median follow-up of 14 months. Thus a salvage attempt with megatherapy in children with resistant or poor prognosis recurrent Wilms' tumor seems to be justified. Drugs such as etoposide and possibly carboplatin have activity in Wilms' tumor, and both could be escalated as part of combination chemotherapy regimens.

Other tumors

High-dose therapy with carboplatin, etoposide, and cyclophosphamide or melphalan have been reported in adults with relapsed high-risk malignant germ cell tumors. As with Wilms' tumor, this usually inherently highly chemosensitive tumor may be a good candidate for this strategy, but experience is limited to a few case reports [128].

There are also case reports of dose escalation in osteosarcoma [11] and in retinoblastoma [129•,130]. Coordinated action would also be warranted for these tumor types as investigators become increasingly interested, demonstrated by 36 patients with osteosarcoma and 30 with retinoblastoma found in the EBMTSTR to date. However, these data are preliminary and inconclusive due to the wide range of indications as well as type of treatments used.

Conclusions

Dose-escalation strategies with and without stem cell support are under intense investigation to improve the prognosis of poor-risk childhood solid tumors. In the absence of new magic drugs, further progress may be expected from a better understanding and use of drug interactions and pharmacokinetics to overcome cell resistance mechanisms. Although almost 20 years have passed since myeloablative megatherapy was first piloted, there still is no proven role for this treatment strategy except for metastatic neuroblastoma. Although phase II data and numerous pilot studies look interesting in terms of response and survival rates, there is an urgent need for international collaboration to design randomized studies that could rapidly address the issue of these expensive and high-morbidity procedures in patients with childhood cancer.

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