Autologous Bone Marrow Transplantation in Paediatric Solid Tumours

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A. Introduction

In leukaemia allogeneic bone marrow transplantation is a method by which high-dose, often curative therapy can be given without regard to marrow toxicity. Applying the same principle to paediatric solid tumours should allow selection of the most active agents for use in combinations, at doses limited only by extramedullary toxicity. The availability of HLA- and DR-matched allografts is very limited, however, restricting this type of marrow transplant to less than one in five children with malignancy. Other options are to use either autologous grafts or mismatched allografts, and at present, autologous bone marrow transplantation (ABMT) is the alternative of choice. ABMT is used either to shorten the period of aplasia after non-ablative high-dose chemotherapy such as melphalan [8] or as a rescue after massive myeloablative chemotherapy, often with total-body irradiation (TBI).

The use of high-dose melphalan in childhood solid tumours was pioneered by the Royal Marsden Group [9], and subsequently a wide variety of multiagent “massive therapy” regimens have been developed. High-dose TBI was introduced by a number of American groups [4, 11] and is now also widely used in European centres. In this review, we consider the application of massive therapy and ABMT to paediatric tumours, with particular reference to the three in which it has been most widely used, namely neuroblastoma (6.2 children/10⁶ population), rhabdomyosarcoma (3.7/10⁶) and Ewing’s sarcoma (2.0/10⁶).

B. Chemo-Radiotherapy Regimens

There are several issues still to be resolved in devising massive therapy protocols. These include determining the effects of extending the time of exposure to a given drug after increasing its absolute concentration and investigating the possible interaction of drugs and irradiation. The choice of agents at high dose has been based either on the known responsiveness of particular tumours at conventional dosage or on theoretical considerations.

Extramedullary toxicity must be balanced against the possible benefits of dose escalation. High-dose therapy inevitably produces toxicity in other organs, particularly the oral mucosa and gastrointestinal tract, which share with the bone marrow a rapid cellular proliferative rate. Also of note are pneumonitis; hepatotoxicity – predominantly veno-occlusive disease; urological toxicity – acute renal failure, haemorrhagic cystitis; neurological complications – leukoencephalopathy, seizures, and cardiomyopathy.

The problems of age and other pre-existing disease encountered in adults are obviously not applicable to paediatric practice, but the extent of initial disease and the nature and complications of previous chemotherapy must be taken into account in anticipating treatment-related complications.

The radiosensitivity of most paediatric tumours is taken advantage of in many conventional treatment regimens, and it is a...
logical step, therefore, to study the efficacy of this treatment modality in high dose. There is an understandable reluctance to use TBI in young children because of the early and, as yet ill-defined, long-term toxicity. Similarly, the advantages of fractionated TBI remain controversial. Although pulmonary toxicity is reduced, the relative cytotoxic effect in tumours with "shouldered" response curves remains to be clarified.

Alternative strategies to TBI are the further intensification of multiple chemotherapy and the use of double autografts [6], but the long-term consequences of high-dose alkylating agents must also be taken into account if these procedures are introduced for other than very poor prognosis patients.

C. Autologous Bone Marrow

One of the major problems associated with autologous transplantation is to ensure that the marrow is free from tumour cells. As many "small round cell tumours" appear similar to normal haemopoietic progenitors on conventional histological and cytological examination, new approaches to the detection of malignant cells in bone marrow have been sought. The ability to produce monoclonal antibodies has greatly enhanced the possibility of detecting tumour cells in bone marrow [7]. The conventional way to define bone marrow status at harvesting is by aspiration or biopsy. Experience in Lyon relating to neuroblastoma has confirmed that biopsies are more effective than aspirates for detecting tumour involvement. Moreover, increasing the number of sampled sites markedly increases the yield of positive results. Even in the absence of demonstrable tumour there may be residual disease, and this provides a rationale for attempting to "purge" the marrow.

Whilst the use of monoclonal antibodies and complement has found favour for purging leukaemic bone marrow, this is not the case for solid tumours. However, a recently reported anti-ganglioside antibody that fixes human complement may have a role here [18].

The drug 4-hydroperoxycyclophosphamide (4-HC) has been used extensively as an agent for destroying leukaemic cells in bone marrow in vitro and has been shown to be active in some human neuroblastoma cell lines. However, although 4-HC has been used in clinical practice, the effectiveness of this procedure still needs to be determined [6].

The most widely applied technique for removing neuroblasts from bone marrow is one employing a cocktail of monoclonal antibodies and magnetic microspheres coated with anti-mouse immunoglobulin. A panel of six anti-neuroblastoma antibodies are used in the procedure to maximize binding to tumour cells and attempt to overcome the problem of antigenic heterogeneity [20].

D. Clinical Results

Neuroblastoma is the most common solid malignancy in early childhood (up to 5 years age). Despite considerable progress in paediatric oncology, neuroblastoma is still a fatal disease for 90% of patients with stage-IV disease (which accounts for at least 70% of cases in children more than 1 year of age). Phase-II studies using high-dose melphalan or chemoradiotherapy followed by ABMT have shown promising response rates [1, 4-6, 15]. Several groups, including ours, have reported preliminary results in cases of stage-IV neuroblastoma using massive therapy and ABMT as an early consolidation procedure for children over 1 year of age, in either partial remission (PR) or complete remission (CR) [6, 13]. A study led by the European Neuroblastoma Study Group (ENSG) is one of the few in which a massive therapy regimen has been evaluated in a prospective randomized fashion. This has demonstrated that in patients with stage-III and -IV disease who received a common initial chemotherapy regimen “OPEC” [19], consolidation with high-dose melphalan increased the duration of relapse-free survival [16]. The southern French cooperative group (LMCE) is currently evaluating a regimen comprised of vincristine infusion, 4 mg/m², melphalan, 180 mg/m², and total-body irradiation with 12 Gy (1200 rads), fractionated at 6 × 2 Gy with lung shielding after 10 Gy. This is given to all stage-IV patients who are over 1 year old at diagnosis and who achieve
at least partial remission within initial chemotherapy.

Of 38 such patients, seven died of toxicity (18%) and 13 relapsed; 18 are alive with NED, with a median observation time of 17 months post diagnosis. Our preliminary conclusions are that this massive therapy is effective in very poor prognosis neuroblastoma (76% response rate in evaluable patients), but that toxicity is high and may be related to the total-body irradiation. This unselected group of patients shows a clear improvement in duration of remission compared with the previous series without ABMT, although long-term survival cannot yet be assessed.

The Villejuif group have studied the use of combination regimens, excluding the use of TBI [6]. A double procedure was used, and autologous marrow was purged with Asta Z. The first regimen comprised carmustine (300 mg/m$^2$), viomycin 26 (1 g/m$^2$) and melphalan (180 mg/m$^2$), and this was repeated 3–4 months later. Of 14 patients thus treated, there were two early toxic deaths and one relapse, and 11 are alive in CR 4–20 months after ABMT (median 12 months). It should be emphasized that these patients were a highly selected subgroup who responded well to initial therapy and were grafted only after extensive staging confirmed CR.

Phase-II studies in children with relapsed or resistant rhabdomyosarcoma have demonstrated a high response rate to high-dose melphalan with autologous marrow rescue (greater than 90%). The duration of response was almost invariably brief, however, with few long-term survivors. As this is a radiosensitive tumour, it seemed appropriate to build on the basis of melphalan and study the value of TBI in such patients. In addition, because the long-term survival of children with stage-IV disease remains poor, massive therapy could be considered for consolidation treatment once CR had been achieved. To date, eight patients (median age 4 years) have been treated in our group: four received massive therapy in first CR, having presented with advanced disease involving metastases of bone in all cases, with or without metastases of marrow, lymph nodes or lungs; two were in second CR after responding to salvage therapy.

Massive therapy comprised vincristine infusion (4 mg/m$^2$ over 5 days), melphalan (140 mg/m$^2$), TBI (12 Gy in six fractions), followed by autologous bone marrow (purged with Asta Z in some patients), or melphalan (120–140 mg/m$^2$) and TBI (9 Gy in a single dose), followed by unpurged autologous marrow. Four patients remain disease free, all of whom were in CR at the time of massive therapy (three first CR and one second CR). Clearly, it is too early to make any firm conclusions about the value of such a procedure or the need to purge the marrow. However, it would appear that, as with most other tumours, one course of massive therapy, even including TBI, is unlikely to salvage patients with progressive or resistant disease.

The use of double procedures is also being studied in rhabdomyosarcoma. In the current International Society of Paediatric Oncology (SIOP) trial, stage-IV patients who achieve CR after chemotherapy alone are randomized (in certain major centres) to receive vincristine, carmustine and melphalan with ABMT (Asta-Z purged), followed after 3–4 months by procarbazine, VP16 and cyclophosphamide. A similar approach is taken for patients less than 5 years old with stage-II/III parameningeal disease who do not receive high-dose cranial irradiation.

In an American series of selected cases with very bad prognosis (relapses, initial stage IV), a combination of vincristine, actinomycin, cycophosphamide and Doxryubicin (adriamycin) (VACA) followed by TBI (8 Gy, 2 fractions) has produced 45% survivors (1 year median follow-up) [10].

In Ewing’s sarcoma, promising preliminary results were obtained by Cornbleet et al. [3] using melphalan as a single agent. In a review of 35 cases in 1984, the European Bone Marrow Transplant (EBMT) Group similarly demonstrated a response rate of 66% in evaluable patients [12]. However, the general pattern of outcome of lymphoma patients after massive therapy is also observed with this solid tumour. The results are good for patients grafted in CR (80% survival at 12 months), reasonable for relapses still responding to rescue protocol (30%), and very poor despite a high response rate for patients grafted in progressive disease. In studies by the NCI of a group of 57 selected very
massive therapy regimen and TBI (8 Gy, 2 fractions, 26 are survivors at 2 year's follow-up.

There are also several reports of the use of ABMT procedures with other tumours such as osteosarcoma [10], Wilms tumour [17], malignant germ cell tumours [2], and glioma [14]. However, the results are too preliminary to comment on the precise role of ABMT in these diseases.

In conclusion, therefore, massive therapy with ABMT is now an established treatment modality in paediatric oncology. The technical aspects and most treatment-related complications have been clarified, and many phase-II studies have shown encouraging results. In the future, management of poor-prognosis diseases such as neuroblastoma may involve the use of more intensive induction regimens to improve the quality of remission at the time of ABMT, which remains the single most important prognostic factor.

References


trosourea (BCNU) and cryopreserved autologous marrow transplantation for refractory cancer. A phase I-II study. Cancer 52:1792-1802


