

Treatment of High-Risk Solid Tumors of Childhood with Intensive Therapy and Autologous Bone Marrow Transplantation

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Although disease-free survival for many children with solid tumors has improved considerably during the past 20 years, it is still poor for a significant number.¹¹⁵ Many patients at risk for failing chemotherapy, surgery, or local irradiation can be identified by clinical staging and other prognostic analyses at diagnosis. Others at high risk for a poor outcome are those who develop progressive disease during or after conventional treatment. These groups of children require new therapeutic strategies that will improve long-term disease-free survival.

Preclinical and clinical data for many tumors indicate that there is a linear-log relationship between drug dose and tumor response, so that a relatively modest increase in dose causes a marked increase in tumor cytotoxicity.^{7, 47, 48, 162-164} For many drugs, particularly alkylating agents, the dose-limiting toxicity is myelosuppression, and higher, potentially more effective doses can be given if this is circumvented. Recent clinical trials in which hematopoietic growth factors were given after non-marrow-ablative chemotherapy suggest that some drug dose escalation is possible if

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This work was supported in part by grants CA22794, CA44904, CA02649, CA53329, and CA12800 from the National Cancer Institute, DHHS, and by the Martell Foundation. LCDR Reynolds is assigned to Children's Hospital of Los Angeles/University of Southern California by the U.S. Navy. The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

hematopoietic recovery is stimulated.⁵ As more growth factors become available and appropriate combinations are identified, this strategy may facilitate administration of even higher doses of drugs. However, the dose of some chemotherapeutic agents and of total body irradiation can be increased well beyond that causing marrow ablation before unacceptable nonhematopoietic toxicity occurs.^{6, 22, 31, 48} Although high-dose, marrow-ablative therapy potentially can increase tumor cell kill and may be curative,^{7, 48, 160} the destroyed marrow must be replaced. Restoration of hematopoiesis by infusion of autologous or allogeneic bone marrow is termed bone marrow transplantation (BMT).^{6, 22, 109, 110, 135, 160, 182}

BMT is a component of combined modality treatment that also includes induction (or reinduction) chemotherapy, and, in most cases, surgery or local irradiation, or both. Surgery, local irradiation, and induction chemotherapy are important for decreasing tumor burden, and the latter may provide an indication of the possible response to subsequent marrow-ablative therapy. Potential effects of the various components of combined modality therapy on tumor cell number are illustrated in Figure 1.

Bone marrow for restoration of hematopoiesis can be obtained from a histocompatible sibling for 20% to 25% of patients and from a histocompatible unrelated donor for less than 10%.¹⁶⁰ By contrast, all patients can potentially donate their own marrow. If metastases are present in the patient's marrow at diagnosis, effective induction chemotherapy is needed to reduce or eliminate them (in vivo purging) before autologous marrow donation. If metastases potentially are present in the donated marrow, most investigators recommend that the marrow be treated ex vivo (marrow purging) to minimize the probability of infusing tumorigenic cells. A general outline of the steps involved in treating high-risk neuroblastoma with

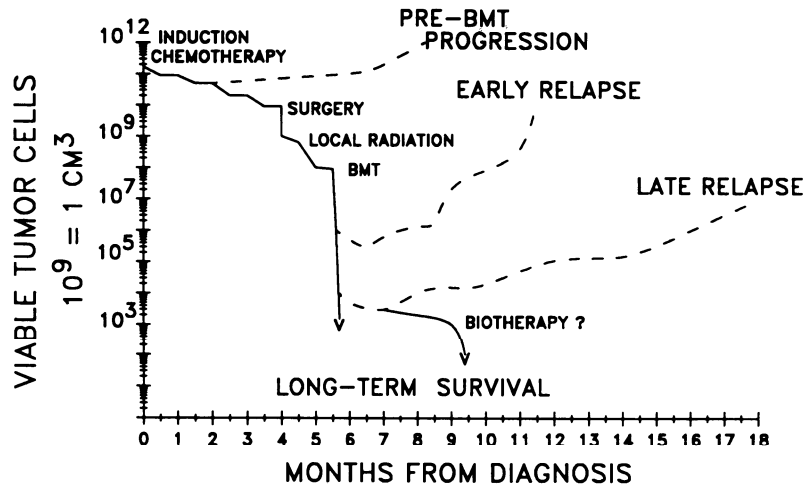


Figure 1. Theoretic neuroblastoma cell kill resulting from induction chemotherapy, surgery, local irradiation, intensive chemoradiotherapy, and post-transplant biotherapy. Five different possible outcomes are illustrated: disease progression during the induction phase; early or late disease progression after marrow-ablative therapy and ABMT; and disease-free survival with or without post-transplant biotherapy.

intensive therapy and autologous BMT is shown in Figure 2. In this review, the abbreviation *ABMT* is used to include both marrow-ablative therapy and autologous marrow infusion.

Restoration of hematopoiesis after marrow-ablative therapy with autologous marrow avoids the risk of graft-versus-host disease (GVHD), which can occur after allogeneic BMT and which can have significant morbidity and mortality.¹⁶⁰ Also, the use of autologous marrow may allow higher dose therapy to be given before BMT because drugs necessary for preventing and treating GVHD contribute to overall therapy-related toxicity.^{11, 143} The

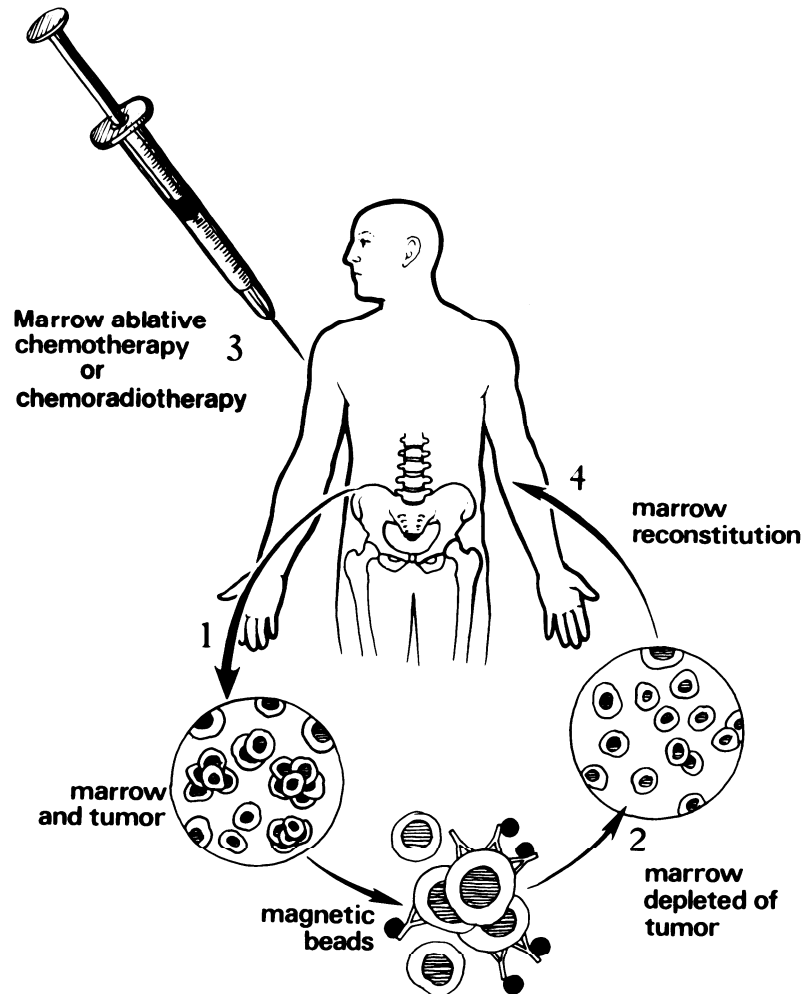


Figure 2. Sequence of events for treating a patient with high-risk neuroblastoma with marrow-ablative chemotherapy or chemoradiotherapy and ABMT. Autologous marrow is harvested and treated ex vivo to remove contaminating tumor cells (steps 1 and 2) and then cryopreserved. Two to 8 weeks later, the patient is given marrow-ablative therapy (step 3), which is followed by infusion of autologous marrow and hematopoietic reconstitution (step 4).

same considerations hold if allogeneic marrow is obtained from a histocompatible (matched) unrelated donor, which currently is associated with a relatively high rate of GVHD and graft failure.¹⁶⁰ The major advantage of allogeneic BMT is that the marrow does not contain any tumor cells; a theoretical advantage, for which there currently is no evidence in childhood solid tumors, is that a graft-versus-tumor effect may occur following allogeneic BMT.

This review discusses ABMT for solid tumors of childhood, including identification of high-risk patients, intensive therapy, and detection and removal of tumor cells from autologous marrow. Results of this therapeutic approach for neuroblastoma and other childhood solid tumors are provided, and new strategies for further improving outcome are considered. General information and specific aspects of bone marrow transplantation not included in this article are provided by a number of recent reviews.^{22, 31, 48, 109, 111, 135, 160, 173, 175, 182}

IDENTIFICATION OF HIGH-RISK PATIENTS

Children with solid tumors who are not likely to achieve long-term disease-free survival with conventional therapy are candidates for ABMT. If ABMT is planned as a component of "frontline" therapy, accurate prognostication at diagnosis is important as it is not appropriate to treat a low-risk patient with intensive therapy. Although nearly all types of childhood solid tumors have high-risk subsets, some can be more accurately identified than others. Subsets having only a 10% probability of survival with current therapy are clearly more homogeneous than those with a 50% likelihood of survival, and results of trials with homogeneous groups are easiest to interpret. In fact, a group of patients with a heterogeneous survival rate should not be included in trials involving ABMT until prognostication is developed that identifies those within the group who have high-risk disease.

Characteristics that can be used to identify high-risk subsets at diagnosis are summarized in Table 1; additional information about prognostication for each tumor type can be found elsewhere.^{41, 115, 136} The most consistent indicator of a poor prognosis is disseminated disease, and so, it is critically important to accurately define the stage of disease at diagnosis.^{19, 39, 91} Histopathology can also provide prognostic information for most types of tumors.^{21, 30, 150} For neuroblastoma, analysis of primary untreated tumors for amplification of the *N-myc* oncogene provides prognostic information that is independent of stage and age at diagnosis; for example, stage II (local) and III (regional) neuroblastomas with genomic amplification of *N-myc* are as aggressive as stage IV (disseminated) neuroblastomas.¹⁴⁰ Prognostic tests based upon such molecular analyses have not yet been developed for other childhood solid tumors.

In contrast to the diversity of newly diagnosed tumors, those that fail to respond to therapy or recur (i.e., progressive disease) currently have poor outcomes,¹¹⁵ and so innovative phase I and II investigations, including ABMT, are warranted. Patients in this group who are most appropriate for

hematopoiesis, many drugs can be escalated well beyond their usual, non-marrow-ablative dose before nonhematopoietic toxicity becomes dose limiting (Table 2), and combining three or more non-cross-resistant drugs at full or nearly full doses has curative potential.^{37, 48} Even if 10^3 to 10^6 tumor cells remain after ABMT, subsequent treatment of the lower tumor load may be successful.

Drug Selection and Dose

Drugs that are appropriate for high-dose therapy with ABMT should have activity for the tumor type, should be tolerable at three to ten times the non-marrow-ablative dose, and should generate a steep and straight-line dose-response curve over many logs of tumor cell kill. Agents that have a shallow or curvilinear dose-response curve, or that have unacceptable nonhematopoietic toxicity after modest escalation, will probably not add efficacy to intensive regimens unless they augment effects of other drugs when given in conventional or nontoxic doses. Preclinical studies in vitro and in tumor-bearing mice can guide selection of drugs and provide dose-response curves, but maximum tolerated dose and antitumor activity must be systematically determined in clinical trials.^{47, 48, 57, 69, 103}

Drug Combinations

As with conventional chemotherapy, the most effective intensive therapy is likely to result from using a combination of three or more agents that are individually effective against a tumor type. In choosing a combination of agents, non-cross-resistance and nonoverlapping toxicities are important considerations. Tumor cells generally do not develop high level resistance to alkylating agents even after prolonged in vitro selection; and when it does develop, resistance to one often does not impart resistance to another.^{47, 48, 162} Attention should also be given to pharmacology and drug interactions that could have antitumor or toxic effects. For example, a nephrotoxic drug given before L-phenylalanine mustard (L-PAM; melphalan) could significantly increase its toxicity as excretion is influenced by renal

Table 2. Chemotherapeutic Agents That Can Be Dose Escalated with Marrow Rescue

DRUG	CONVENTIONAL DOSE (mg/m ²)	ABMT DOSE (mg/m ²)	MAJOR NONHEMATOPOIETIC TOXICITY
Cyclophosphamide	1000	7500	cardiomyopathy
L-PAM	40	225	mucositis
Carboplatin	400	2000	hepatic, renal
Etoposide	300-600	2400	mucositis
Thiotepa	20-50	1125	mucositis, CNS
Busulfan	2	450	hepatic
Carmustine	200	1200	pulmonary, hepatic
Ifosfamide	5000	18000	renal

Doses are approximate and are for drugs as single agents. When combinations are used, doses may need to be decreased.

Data from Eder JP, Elias A, Shea TC: A phase I-II study of cyclophosphamide, thiotepa and carboplatin with autologous bone marrow transplantation in solid tumor patients. *J Clin Oncol* 8:1239-1245, 1990.