

Table 1. Induction Therapy

Week										
0	4	8	12	13	17	18	21	22	26	
CDEC*	CDEC	CDEC	Bone marrow harvest†	CDEC	Surgery to residual disease	CDEC	Radiation to residual disease	CDEC‡	Ablative chemotherapy, TBI, and BMT§	

NOTE. Chemotherapy was repeated every 28 days for 5 or 6 cycles, with bone marrow harvest after the third or fourth cycle, delayed primary surgery after the fourth or fifth, and local radiation therapy to bulk residual disease after the last cycle before BMT.

\*CDEC = cisplatin 60 mg/m<sup>2</sup> per 6 hours, day 0; doxorubicin 30 mg/m<sup>2</sup>, day 2; etoposide 100 mg/m<sup>2</sup> per 1 hour, days 2 and 6; cyclophosphamide 30 mg/kg, days 4 and 5.

†For autologous BMT.

‡Optional if delay necessary for timing of BMT.

§Recipients of allogeneic BMT received methotrexate intravenously 5 mg/m<sup>2</sup> on days +1 and +4.

by Shimada classification, genomic amplification of *N-myc* (> 10 copies), or serum ferritin level more than 142 ng/mL.<sup>12-15</sup> Appropriate informed consents for the initial chemotherapy induction protocol and the subsequent allogeneic or autologous BMT were obtained according to the requirements of local institutional review boards.

### Induction Therapy

All patients included in this comparison received induction therapy according to a group-wide chemotherapy pilot study, CCG-321P2. Thus, although any patient who met the criteria for progression-free high-risk neuroblastoma stated below could be treated on the allogeneic or autologous BMT protocols, for the purposes of this comparison, only patients who received the identical induction therapy and pre-BMT ablative therapy described later were included. The treatment consisted of five or six cycles of chemotherapy,<sup>16</sup> autologous bone marrow harvest, purging, cryopreservation (for the autologous group), surgical resection of the primary tumor, and local radiation to sites of persistent disease (Table 1). Surgical resection of the primary tumor was attempted after four cycles of chemotherapy, followed by local irradiation if resection was incomplete. A dose of 20 Gy was administered to residual primary or metastatic sites, except for intraabdominal disease, for which the dose was 10 Gy to reduce toxicity resulting from the subsequent high-dose chemotherapy and TBI. Evaluation of disease status was performed within 2 weeks before BMT, including appropriate imaging studies of primary tumor (magnetic resonance imaging or computed tomography), bone scan, bilateral bone marrow aspirates and biopsies, and immunocytology. CCG and international response criteria were used for disease status.<sup>17</sup>

### Eligibility for Allogeneic or Autologous BMT

Patients were eligible for intensive chemoradiotherapy and BMT provided they met diagnostic and risk group criteria, had not developed progressive disease, had normal organ function, and were less than 36 weeks from diagnosis at the time of BMT. BMT was not mandatory, and the decision whether to continue chemotherapy or to proceed to BMT was by investigator and parental choice. Any patient who had a human leukocyte antigen (HLA)-compatible sibling was eligible for allogeneic BMT (CCG-321P1), while those high-risk neuroblastoma patients who had no donor were eligible for autologous BMT (CCG-321P3).

CCG-321P1 was a group-wide pilot study of allogeneic BMT for neuroblastoma patients that was open to entry for this patient cohort from November 1988 to July 1991. CCG-321P3 was a limited-

institution pilot study of autologous BMT for neuroblastoma that was open to patient entry for this patient cohort from September 1988 to September 1990. For both studies, patients received induction therapy at their local institution and were then referred to any CCG transplant institution for 321P1 or to a participating institution for 321P3. The cutoff date used for analysis was July 18, 1993.

### Autologous Bone Marrow Purging

After three to five cycles of chemotherapy (when bone marrow tumor content was < 2%), bone marrow was harvested and treated *ex vivo* to remove tumor cells using hetastarch sedimentation, filtration, and immunomagnetic beads, and then cryopreserved.<sup>7,18</sup> All bone marrow samples were harvested, purged, and cryopreserved at the CCG Neuroblastoma Bone Marrow Purging Laboratory at Childrens Hospital Los Angeles. All marrow samples used for autologous BMT were evaluated by immunocytology (sensitivity, one tumor cell per 100,000 nucleated bone marrow cells)<sup>10</sup> after purging and found to be free of detectable tumor cells.

### Treatment Protocol

Patients who were progression-free and elected to receive BMT were treated with high-dose chemotherapy and TBI (Table 2) followed by HLA-matched sibling bone marrow or autologous purged bone marrow infusion. Recipients of allogeneic BMT received methotrexate for GVHD prophylaxis on days 1 and 4 post-BMT, but at a dose of only 5 mg/m<sup>2</sup>/d, which was reduced to decrease the toxicity of the overall regimen. Methotrexate levels were monitored at 24 hours and leucovorin administered for levels greater than 5 × 10<sup>-8</sup> mol/L. Patients were evaluated for disease status 1 month posttransplantation and then every 3 months.

### Statistical Analysis

Life-table methods<sup>19</sup> were used to estimate the progression-free survival (PFS) from time of BMT. The log-rank statistic was used to compare the PFS probabilities between patient subgroups. In the analysis of the probability of relapse, patients who died of causes other than progressive disease, such as infection or therapy-related toxicity, were kept in the construction of the life-tables, but they were censored at the time of death. Relative risk analysis was performed using the regression method of Cox.

## RESULTS

### Patient Characteristics

Fifty-six patients (20 allogeneic and 36 autologous) were transplanted between September 1988 and July