

in the allogeneic group, probably due to the use of methotrexate post-BMT and to GVHD. However, there was no overall significant difference in the percentage of patients with grade 3 and 4 toxicity who received allogeneic or autologous BMT, and no predominant cause of toxic death.

The reconstitution of neutrophils was more rapid with allogeneic than autologous BMT, although the use of granulocyte-macrophage colony-stimulating factor after autologous BMT in subsequent protocols has abrogated this difference. The platelet engraftment was also significantly more rapid for allogeneic than autologous BMT, which may be related either to cell dose or to the effect of cryopreservation on bone marrow progenitors.^{24,25}

Contrary to what would be expected if tumor-cell reinfusion with the marrow were a problem, the relapse rate was lower in the autologous group than in the allogeneic group, although this difference was not significant ($P = .14$), and not different from the 36% relapse rate reported by Dini et al.²² There are several possible explanations for this difference in relapse rate observed in the current study. First, physician or parent bias may have influenced the decision to use myeloablative therapy, since there was a choice of continuing chemotherapy or proceeding to BMT. Second, there was a significantly higher proportion of patients with *N-myc*-amplified tumors in the allogeneic group (58 v 20%; $P = .03$). This may be just an apparent difference, since this information was available for only about half of each group. Even if this is a real difference, we and others have shown no difference in outcome after autologous BMT for groups of patients whose neuroblastomas are *N-myc*-amplified or nonamplified.^{20,26-28} This is in contrast to prior chemotherapy studies, in which *N-myc* gene amplification has been an unfavorable prognostic factor.¹⁵ Third, there was a small but significant ($P = .002$) decrease in time from diagnosis to BMT in the allogeneic group (6.5 months) compared with the autologous group (7.8 months). This may have represented administration of an additional course of induction therapy in some autologous patients, necessitated by the logistics of bone marrow harvest. Fourth, it is possible that more favorable patients were in the autologous group, since only patients who responded enough to induction therapy to reduce bone marrow tumor content to less than 2% for the purging process underwent bone marrow harvest. However, there was no significant difference between the groups in percentage with bone or bone marrow disease at diagnosis, overall tumor response at BMT, or in marrow tumor content at diagnosis or pre-BMT. However, the three patients in the allogeneic group with detectable tumor at the time of BMT all had greater than 0.1% tumor cells, compared with the six patients in

the autologous group with detectable tumor, who all had less than 0.1% tumor content. The percentage of patients in CR plus VGPR was similar in the two groups (52% v 55%), and the overall complete response rate in the allogeneic group at the time of BMT was actually higher than that of the autologous group (45% v 26%), although this difference was not statistically significant. When only patients in CR at the time of BMT are considered, the 4-year event-free survival rate is significantly higher in autologous patients (57%) than allogeneic BMT patients (27%). However, since four of the 8 events in the allogeneic group of 11 patients in CR or VGPR were toxic deaths, the relapse rate in the two groups is not significantly different. Only two of the eight events that occurred in the 19 autologous patients in CR or VGPR were toxic deaths. Thus, approximately one third of patients in CR or VGPR relapsed, regardless of type of BMT.

There is no evidence in the current study that tumor cells in reinfused bone marrow contribute to relapse. We purged the marrow with a combination of hetastarch sedimentation, filtration, and immunomagnetic beads, which may remove 4 to 5 logs of tumor cells.¹⁸ It is still theoretically possible to infuse tumor cells remaining below our current level of detection, which is one tumor cell per 100,000 nucleated bone marrow cells. The one relapse in lung, an unusual site of metastasis in neuroblastoma and a site that would be expected from intravenous tumor-cell infusion, occurred in a patient in the autologous group. Similar cases of spread have been reported in cases of known tumor-cell reinfusion.^{8,9} The rate and sites of relapse after purged autologous or allogeneic BMT in our study were similar, which makes it difficult to incriminate tumor-cell reinfusion. However, this does not preclude the possibility that unpurged or inadequately purged marrow containing tumor cells can cause relapse.

We conclude that the toxicity of allogeneic BMT is not significantly different from autologous purged BMT for neuroblastoma. Neither is the relapse rate significantly different for the two groups. Last, the PFS rate is higher, although not significantly so, for autologous than allogeneic BMT ($P = 0.051$), with a 95% confidence interval for PFS for autologous BMT of 26% to 108% that of allogeneic BMT. Thus, although caution must be used in interpretation of a retrospective, nonrandomized comparison, outcome after autologous purged BMT appears to be equivalent to allogeneic BMT following myeloablative therapy for high-risk neuroblastoma.

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