

High-dose Chemotherapy for Recurrent Medulloblastoma

Time for a Reappraisal

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More than a decade ago, Finlay et al. published a landmark article in which they demonstrated that a subset of patients with recurrent brain tumors of diverse histologic diagnosis could be salvaged with high-dose chemotherapy followed by autologous stem cell rescue.¹ The preparatory regimen included only 2 drugs: thiotepa and etoposide. Hematopoietic growth factors were used to enhance count recovery. Observations from this early series suggested that patients with minimal residual disease at the time of high-dose chemotherapy may be the appropriate candidates for this retrieval strategy. Patients with bulky, metastatic recurrent disease or disease that has not responded to retrieval chemotherapy may not be the best candidates for this intervention. The toxicity of this approach was also a concern in this early series. Overall, 5 of the 45 patients (11%) were long-term survivors and all of them had high-grade gliomas.

Subsequent publications from these and other investigators have further defined the role of high-dose chemotherapy in patients with recurrent medulloblastoma.²⁻⁴ Dunkel et al. suggested that patients treated with prior combined modality therapy (ie, radiotherapy and chemotherapy) had a worse outcome compared with patients who were treated with chemotherapy only ($25 \pm 15\%$ vs $43 \pm 16\%$).² In the series by Gururangan et al., 12 of the 20 patients (60%) were irradiated after high-dose chemotherapy and autologous bone marrow rescue and 7 of these 12 patients were long-term survivors.³ Taken together, these data suggest that a select group of patients may be able to achieve durable disease control; this subgroup consists of young patients treated with chemotherapy alone as initial therapy followed by high-dose chemotherapy and radiotherapy at the time of disease recurrence. In a large prospective French series, infants with local recurrences of medulloblastoma after initial treatment with surgical resection and chemotherapy alone could be salvaged with surgical resection, high-dose chemotherapy, and radiotherapy. In contrast, patients with metastatic recurrent disease had a much worse outcome.⁴

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Mahoney et al.⁵ used a cyclophosphamide-based, high-dose chemotherapy regimen and confirmed in a prospective series that patients with minimal residual disease who are responsive to chemotherapy are the patients most likely to benefit from high-dose chemotherapy at the time of disease recurrence. Based on the encouraging data in pediatric patients with recurrent medulloblastomas, the adult neuro-oncology community has adopted high-dose chemotherapy as an approach in the treatment of adult patients with recurrent embryonal tumors. In this issue of *Cancer*, Gill et al. demonstrated, in a retrospective institutional series spanning 31 years, that patients with recurrent medulloblastoma who are treated with high-dose chemotherapy and autologous stem cell transplantation enjoy a longer duration of disease control and overall survival compared with patients treated with standard-dose chemotherapy at the time of disease recurrence.⁶ The authors pointed out the inherent problems with their study and recognized the difficulties in conducting an adequately sized, prospective, randomized trial in adults, given that this disease is rare in this age group. However, several important observations of their study population are worth noting. All the patients in their series were treated with surgical resection and radiotherapy alone as part of their original treatment. In addition, not all patients were treated with craniospinal irradiation; some patients were treated with cranial irradiation only (5 patients). Unlike the treatment of children, in whom combined modality therapy is considered the standard of care,⁷ radiotherapy alone is commonly used in the treatment of adult medulloblastoma patients. Hence the finding that the patients included in the series by Gill et al.⁶ were chemotherapy-naïve may have tipped the scales in favor of chemotherapy as a retrieval strategy for patients with recurrent disease.

The burden of bulky metastatic disease in the neuraxis (5 patients) and extraneural disease (4 patients) was much higher in the group treated with conventional-dose chemotherapy compared with 1 patient with neuraxis dissemination and 3 patients with extraneural disease in the group treated with high-dose chemotherapy.⁶ Although 54% of the patients treated with conventional-dose chemotherapy received some form of repeat irradiation at the time of recurrent disease, no patients in the high-dose chemotherapy group received additional radiotherapy. Lastly, 50% of the patients in the high-dose chemotherapy group underwent macroscopic total resection at the time

of disease recurrence compared with 1 of the 13 patients in the group treated with conventional-dose chemotherapy.⁶ In summary, the factors that are believed to be important predictors of outcome in pediatric patients with recurrent medulloblastoma could not be evaluated in this adult series because of the retrospective nature of the study. These include 1) minimal residual disease at the time of transplantation, 2) local recurrence, 3) chemotherapy-responsive disease, 4) the use of radiotherapy after high-dose chemotherapy, and 5) patients who are minimally treated at the time of the original diagnosis. Hence, the conclusions from the study by Gill et al. are to be interpreted with caution.

Our current understanding of the pathogenesis of medulloblastoma is undergoing a rapid and dramatic transformation because of the discoveries of important signal transduction pathways that are responsible for normal development of the cerebellum.⁸ There also are early data to indicate that medulloblastoma is not a single disease entity but actually consists of a compendium of different, molecularly distinct diseases that may have a similar morphologic appearance under the microscope.⁹ Based on these discoveries, there is a possibility that in the future we will not be treating medulloblastoma as a single disease entity. Instead, we may well be tailoring our therapy to the underlying molecular aberrations and hence increasing our chances of cure with minimally toxic therapy and reducing the possibility of long-term morbidities.¹⁰

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