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Management of late extraneural recurrence of medulloblastoma without high-dose chemotherapy

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To the Editor

Medulloblastoma is the most common primary brain tumor in children, though in adults it represents only 1 % of primary brain tumors. Extraneural recurrence of medulloblastoma is rare, and there is no standard regimen for treatment. Standard dose chemotherapy using cyclophosphamide, adriamycin, and vincristine showed a median time to progression of 17 months in a case series of 7 patients [1]. Our group previously reported efficacy of high-dose chemotherapy with autologous stem cell rescue (ASCR) in a series of 23 patients with previously irradiated recurrent medulloblastoma [2]. Indeed, a similar approach using Ewing Sarcoma protocol in addition to ASCR was effective for extraneural recurrence in an adult [3]. Here, we report an additional less toxic approach, with standard dose chemotherapy, which successfully induced long-term remission of extraneural recurrence in an adult.

Our patient was diagnosed with medulloblastoma in the left cerebellum at the age of 22. She underwent gross total resection and craniospinal radiation with a boost to the primary site. No ventriculoperitoneal shunt was required. Surveillance imaging with MRI over the next 14 years showed no evidence of recurrent tumor. Some 17 years after the discovery of the initial tumor, the patient developed a right supraclavicular mass measuring $4.3 \times 7.2 \times 4.5$ cm. Biopsy showed malignant small blue cells, immunoreactive for synaptophysin and neuron specific enolase; highly resembling the original tumor and consistent with recurrent medulloblastoma. MRI of the brain and spine showed no recurrence in the central nervous system. Lumbar puncture showed no malignant cells in the CSF. PET and CT scan showed no additional focus of metastatic disease.

We treated our patient with a total of 6 cycles of chemotherapy; cycles of cisplatin (75 mg/m^2 for 1 day) and etoposide (100 mg/m^2 for 2 days) alternating with cycles of cyclophosphamide (2100 mg/m^2 for 2 days) and topotecan (2 mg/m^2 for 4 days). Notable toxicities were: grade 3 infection, grade 4 thrombocytopenia, and grade 3 mucositis. Following chemotherapy, MRI showed a reduction in mass size and PET showed decreased FDG avidity. Chemotherapy was followed by resection of the supraclavicular mass. She subsequently underwent intensity modulated radiation therapy to the supraclavicular region

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with a total of 45 Gy. Serial yearly MRI scans of the brain and neck have showed no evidence of recurrence, now 6 years since treatment.

In a previous study from our group evaluating high-dose chemotherapy with ASCR in recurrent medulloblastoma [2], none of the patients with M-4 medulloblastoma were event-free survivors post-ASCR. An additional study from our center showed that adults with brain tumors treated with high-dose chemotherapy with ASCR seemed to have a greater risk of treatment-associated mortality than children; between 18 and 25 % of patients, depending on the chemotherapy agent used, most frequently from multi-organ failure [4]. There was a marked trend toward increased mortality in individuals over the age of 30, although as the series was small this did not reach statistical significance [4]. On the basis of these data, we opted to treat our patient with a standard-dose chemotherapy regimen prior to resection and radiation therapy.

The biology of extra-late recurrence (>15 years) in medulloblastoma and specifically, why cancerous cells remain at sub-clinical numbers for such long periods is not well understood. Given the rarity of late extraneural recurrence in medulloblastoma, deciding optimal treatment is a clinical challenge, and can be guided by experiences from single cases. We present here an additional regimen which was effective in the management of isolated extraneural recurrence, and may be an approach which avoids the relatively high risk of mortality observed with use of high-dose chemotherapy and ASCR in adults with brain tumors.

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