Chronic Residual Lesions in Metastatic Medulloblastoma Patients

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Summary: In a retrospective review of 24 metastatic medulloblastoma patients whose treatment included craniospinal irradiation, 5 patients presented with gross residual abnormalities at completion of therapy. This report describes 2 medulloblastoma patients with persistent residual abnormalities on serial follow-up imaging studies. The patients aged 2 and 2.5 years old at the time of diagnosis underwent surgery followed by multiagent chemotherapy and received low-dose craniospinal irradiation. The second showed residual tumor on end of treatment imaging and received low-dose craniospinal irradiation. Despite persistent magnetic resonance imaging findings, the patients are alive and well 13 and 7 years after diagnosis with no further treatment applied. The nature of these residual abnormalities is discussed.  

Key Words: pediatric, medulloblastoma, residual lesions  

J Pediatr Hematol Oncol 2014;36:71–75  

Medulloblastoma is the most common malignant brain tumor in childhood. Progress in surgery and radiation techniques and the introduction of chemotherapy in the early 80s have contributed to a gradual improvement in treatment outcome. Five-year survival rates in average-risk patients approach 85%, whereas survival rates in high-risk patients increased from 40% to nearly 70% in some recent reports. Still, results of treatments in infants and young children are inferior due to the reluctance to use craniospinal irradiation in this age group.  

Treatment for medulloblastoma is aiming at complete eradication of disease. Close follow-up with regular imaging during and after treatment is an essential component of all current protocols, with stable or progressive disease interpreted as treatment failure. Data regarding outcome of patients with residual disease on imaging after treatment are scarce and whether incomplete response on imaging is compatible with long-term survival is still unclear.  

We present 2 cases of young patients diagnosed with medulloblastoma with macrometastatic residual disease on imaging at completion of therapy. Both patients are alive with no further treatment and no change on serial imaging studies over a period of 13 and 7 years.  

MATERIALS AND METHODS  

With the approval of the Research and Ethnic committee of the Hospital for Sick Children, we reviewed data of medulloblastoma patients for the period 1999 to 2009. The purpose of the review was to identify patients with metastatic medulloblastoma who had obvious residual disease at completion of treatment and to assess their outcome. Selection criteria were (1) patients diagnosed with medulloblastoma with evidence of metastatic disease on magnetic resonance imaging (MRI) scan (M2 and M3 patients); (2) management that included surgery, craniospinal radiation with or without chemotherapy; (3) evidence of macroscopic (>1 cm²) residual radiologic abnormalities in areas of previous disease sites (primary tumor or previous metastatic sites) at completion of therapy.  

RESULTS  

During the period 1999 to 2009, 24 medulloblastoma patients fulfilled eligibility criteria 1 and 2. Three patients showed tumor progression while on postradiation maintenance chemotherapy therapy. Seventeen patients completed therapy in complete response or near-complete response (2 patients with residual linear spinal enhancement). Five patients, all with diffuse metastatic disease at presentation, had residual abnormalities > 1 cm² in previous disease sites. Three patients (aged 4, 5, and 9 y old at the time of diagnosis) eventually showed clinical and radiologic progression at 12, 3, and 1 months, respectively, after completion of therapy and died of refractory disease. However, 2 patients with extensive residual abnormalities did not show evidence of progression and are described herein.  

Case 1  

A 2-year-old child was seen for a short history of irritability and ataxia. MRI demonstrated multiple posterior fossa lesions including lower brain stem lesions extending to the spinal cord with local infiltration. Biopsy revealed a highly cellular lesion consistent with primitive neuroectodermal tumor/medulloblastoma, with abundant mitotic figures, foci of necrosis, and mineralization. Because of young age, the decision was made to treat with chemotherapy only. The child was treated according to the institutional guidelines with a 4-drug regimen using cisplatin, cyclophosphamide, vincristine, and VP-16 as per POG 8633 protocol. After 9 months of chemotherapy, MRI scan showed significant progression. The child underwent salvage craniospinal irradiation at a dose of 41.4 Gy with boost to the posterior fossa of 14.40 Gy. The end of treatment brain MRI scan demonstrated significant...
improvement. However, residual lesions were still seen in the cerebellopontine angle and on the floor of the third ventricle. The spinal MRI revealed leptomeningeal enhancement with multiple extradural enhancing lesions surrounding the spinal cord and cauda equina. No further treatment was considered. Over the last 10 years, the child was followed closely. No signs of tumor progression were seen either clinically or on imaging during that time. Repeat MRI scans demonstrated considerable residual abnormalities at the brain and the spinal level, although some shrinkage was observed overtime (Figs. 1A, B). After treatment, the child had significant neurocognitive impairment that required special educational program. Thyroid replacement therapy was started 4 years after end of treatment. Despite growth hormone deficiency, hormonal replacement was deferred due to parental concerns regarding growth hormone treatment in the setting of significant residual disease. Growth hormone along with GH-RH analog to suppress pubertal development were started 9 years after diagnosis, with height approaching the 50th percentile on last follow-up, and still significant residual lesions on imaging. Molecular characterization of the tumor was impossible to the lack of available tissue.

**Case 2**

A 2.5-year-old child was admitted after a 7-day history of occipital headache, morning vomiting, and ataxia. The child had no significant medical issues in the past, and family history was negative for cancer. MRI demonstrated multiple spinal and posterior fossa lesions along with a lesion in the suprasellar region. The patient underwent excisional biopsy of a superficial nodule at the surface of the cerebellum with concomitant insertion of a ventriculoperitoneal shunt. Cerebrospinal fluid from the ventricle was negative for malignant cells. Pathology was consistent with medulloblastoma with different areas in the tumor expressing variable MIB-1 reactivity and expression of P53. The child was started on treatment according to the Head Start II protocol with 5 cycles comprised of methotrexate, cisplatin, VP-16, vincristine, and cyclophosphamide followed by high-dose chemotherapy (HDCT) with autologous stem cell support. After 5 cycles of intensive chemotherapy, repeat MRI showed partial response. The MRI scan at completion of HDCT demonstrated persistent disease in the posterior fossa, in the suprasellar region and along the spine. The patient underwent craniospinal radiation at a dose of 21.6 Gy with boost to the posterior fossa to a total dose of 50.4 and boost to the spine to a total dose of 36 Gy. Follow-up MRI scans on the last 5 years revealed only slight decrease in size of the residual lesions or in their pattern of enhancement (Fig. 2). In an effort to evaluate viability of residual lesions, the patient underwent a fluorodeoxyglucose positron emission tomography 3 years after diagnosis. The suprasellar lesion did not show any uptake.
but the lesion on the posterior fossa was weakly positive. No clear conclusion could be drawn regarding the activity of these residual masses. Seven years after diagnosis, the child is clinically well. She is in a special needs program with educational assistance. Endocrine testing revealed isolated growth hormone deficiency. Replacement therapy was started 3 years after diagnosis with still significant residual abnormalities on imaging after 3 year of growth hormone therapy. On a recent analysis of the medulloblastoma subtype, the tumor was falling in the group 3 category of the consensus classification.10

**DISCUSSION**

Imaging response is rarely reported in medulloblastoma studies and the meaning of residual disease at completion of therapy is still unclear. Within the few studies reporting posttreatment imaging results, residual tumor appears to be found in a significant number of the patients. Gajjar and colleagues reported the response and outcome of 42 high-risk medulloblastoma patients treated on the SJMB96 protocol, with craniospinal radiation of 36 Gy, followed by 4 consecutive cycles of HDCT. Eighteen of the 42 (42%) patients had residual findings on MRI 1 month after completion of therapy. Five-year event-free survival estimate in this high-risk group was 70%, but no correlation was provided between outcome and presence or absence of residual MRI findings at completion of therapy.3

In another report on salvage HDCT in infants and young children, 4 of 20 patients had measurable disease on MRI after surgery and focal radiotherapy. None of these patients survived.11 In our experience, 5 patients out of 24 with metastatic disease at diagnosis had residual disease at completion of therapy. Interestingly, the 2 patients who did not show progression were the younger patients.

Residual findings, demonstrated on MRI, may be the end product of multiple processes including stable/progressive disease, scar tissue replacing the original malignancy, residual viable tumor with different degrees of maturation, or treatment effect on normal brain tissue.

Several medulloblastoma studies described transient radiologic changes in normal brain tissue following chemoradiation protocols, particularly after HDCT.12,13 However, such changes are new, transient, and essentially located in the periventricular/brainstem white matter. Posttreatment residual findings could represent scar tissue, as reported in other pediatric malignancies such as Hodgkin disease or rhabdomyosarcoma.14,15 Presence of such fibrotic remnants has no effect on patients’ outcome in these reports. Among studies that have evaluated the prognostic value of residual findings on MRI of medulloblastoma patients on treatment, presence of residual tumor at the end of induction and before consolidation with HDCT was repeatedly found to confer worse prognosis, suggesting presence of active malignant cells within tumor residual.7,9,11,16

**FIGURE 2.** Patient 2: End of treatment MRI showing residual abnormalities in the suprasellar region and the posterior fossa (A). MRI scan 5 years later showing persistent abnormalities in both areas (B). MRI indicates magnetic resonance imaging.
chemotherapy. However, the 2 tumors in our experience did not show evidence of medulloblastoma with extensive nodularity features, and the molecular characterization of the tumor in patient 2 was not in keeping with this diagnosis.

Differentiation and maturation of residual tumor may explain prolonged survival of patients with residual post-treatment imaging findings. Kushner and colleagues presented extremely prolonged course of disease in 36 patients with high-risk neuroblastoma. Tumor maturation was suggested as one possible explanation but supporting data from pathologic specimens were limited. No biopsy was done in our experience, although its potential benefit in guiding treatment decisions was discussed in multiple occasions. However, because of the disseminated aspect of residual abnormalities this would have required multiple surgeries at different critical locations (cerebellopontine angle, third ventricle, and spine in patient 1; spine, posterior fossa, and suprasellar region in patient 2). The persistence of contrast enhancement was in both cases more suggestive of active residual tumor, as maturation is usually associated with disappearance of contrast uptake. The use of positron emission tomography imaging in patient 2 did not provide helpful conclusions, as it showed a weak uptake in the posterior fossa, suggestive of residual active disease, despite stable MRI findings 2.5 years after completion of treatment. The role of other imaging techniques, in particular MR spectroscopy, to assess such residual abnormalities is still unknown.

These observations raise the possible benefit of the use of differentiating agents in patients with residual findings at completion of therapy. The role of retinoid therapy—known to induce cytodifferentiation and inhibit cell proliferation in several malignancies—was evaluated in 2 preclinical studies. Chaw and colleagues evaluated the effect of all trans retinoic acid on 3 medulloblastoma cell lines. Cell growth arrest was demonstrated in one of the cell lines with decreased expression of CyclinD1 and C-Myc. Spiller and colleagues evaluated the effect of cis retinoic acid with and without SAHA, a histone deacetylase inhibitor on cell cultures and in animal models. Mice treated with retinoic acid with and without SAHA showed a 4-fold increase in apoptosis over controls. The only treated with retinoic acid + SAHA + cisplatin showed the effect of all trans retinoic acid on 3 medulloblastoma cell lines. Growth inhibition was demonstrated in one of the cell lines with decreased expression of CyclinD1 and C-Myc.

CONCLUSIONS

We describe 2 cases of children with high-risk medulloblastoma and significant residual findings on imaging after completion of treatment. These 2 children were followed for 13 and 7 years with no clinical progression or change in imaging. The possibility of having residual findings on imaging with no clinical implication should be taken under consideration when offering treatment for these patients. Either biopsy of the lesions or close follow-up should be encouraged, to prevent overtreatment and misinterpretation of treatment results.

REFERENCES


