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Low Incidence of Radionecrosis in Children Treated with Conventional Radiation Therapy and Intrathecal Radioimmunotherapy

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Abstract

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Radionecrosis is a potentially devastating complication of external beam radiotherapy (XRT). Intraventricular compartmental radioimmunotherapy (cRIT) using ^{131}I -3F8 or ^{131}I -8H9 can eradicate malignant cells in the CSF. The incidence of radionecrosis using cRIT ^{131}I based intraventricular radioimmunotherapy, when used alone or in combination with conventional craniospinal CSI-XRT is unknown. We retrospectively analyzed the incidence of radionecrosis in 2 cohorts of pediatric patients treated with both CSI-XRT and cRIT at MSKCC since 2003: patients with metastatic CNS neuroblastoma (NB) and medulloblastoma (MB). 94 patients received both CSI-XRT and cRIT, 2 received cRIT alone, median follow up 41.5 months (6.5–124.8 months). Mean CSI-XRT dose was 28 Gy (boost to the primary tumor site up to 54 Gy) in the MB cohort, and CSI XRT dose 18–21 Gy (boost to 30 Gy for focal parenchymal mass) in the NB cohort. For MB patients, 20% had focal re-irradiation for a second or more subsequent relapse, mean repeat-XRT dose was 27.5 Gy; 7 patients with NB had additional focal XRT. Median CSF cRIT dose was 18.6 Gy in the MB cohort and 32.1 in the NB cohort. One asymptomatic patient underwent resection of 0.6-cm hemorrhagic periventricular white-matter lesion confirmed to be necrosis and granulation tissue, 2.5 years after XRT. The risk of radionecrosis in children treated with XRT and cRIT appears minimal (~1%). No neurologic deficits secondary to radionecrosis have been observed in long-term survivors treated with both modalities, including patients who underwent re-XRT. Administration of cRIT may safely proceed in patients treated with conventional radiotherapy without appearing to increase the risk of radionecrosis.

Keywords

Pediatric oncology; brain tumors; radiation therapy; intrathecal therapy; side effects

Introduction

Radionecrosis is a potentially devastating long-term complication of external-beam radiotherapy (XRT) including craniospinal radiation therapy (CSI), with a reported incidence in some series as high as 5%. [1, 2] Suspicious radiographic lesions are initially noted on consecutive MRIs taken at various intervals. The diagnosis of radionecrosis is ultimately based on a combination of clinical, radiological and dosimetric criteria, typically confirmed by histopathology. Intraventricular compartmental radioimmunotherapy (cRIT) using ^{131}I -3F8 or ^{131}I -8H9 monoclonal antibodies has been used to eradicate malignant cells in the cerebrospinal fluid (CSF) space, with no long term neurologic toxicity. [3, 4] The incidence of radionecrosis among children with malignant brain and/or spinal (CNS) tumors treated with XRT, CSI, and cRIT is unknown.

Methods

We performed a retrospective single-center study analyzing the incidence and clinical course of radionecrosis in patients treated with CSI-XRT with focal parenchymal boost and cRIT at Memorial Sloan Kettering Cancer Center (MSK) since 2003. A waiver for collection of patient data was approved by the MSK IRB. Patients in this analysis had a histopathologically confirmed diagnosis of recurrent/high risk-medulloblastoma (MB) or neuroblastoma (NB) metastatic to the brain parenchyma, spinal cord, or leptomeninges.

Patients with medulloblastoma received conventional CSI as part of upfront therapy at initial diagnosis (CSI-XRT 23.4 Gy for patients with standard-risk disease and 36 Gy for patients with high-risk disease.) All patients with MB received an initial boost to the primary tumor bed to 54 Gy. Patients with metastatic CNS NB were treated with CSI-XRT up to 21.6 Gy, with an additional boost up to 9 Gy to focal metastatic lesions as previously described.[3]

cRIT Therapy

Patients were enrolled on an IRB-approved protocol testing cRIT with ^{131}I -3F8 (NCT00445965), or ^{131}I -8H9 (NCT00089245) for individuals with high-risk metastatic CNS tumors. For both trials, patients had to meet eligibility criteria: having a refractory or recurrent neuroblastoma or medulloblastoma with a predilection for leptomeningeal dissemination. Tumors were known to express GD2 for 3F8, or 8H9 reactivity by immunohistochemistry. Eligible patients had no rapidly deteriorating neurologic examination or obstructive hydrocephalus, an absolute neutrophil count $> 1000/\text{ul}$, platelet count $> 50,000/\text{ul}$, blood urea nitrogen $< 30 \text{ mg/dl}$, serum bilirubin $< 3.0 \text{ mg/dl}$, and serum creatinine $< 2 \text{ mg/dl}$. For patients receiving cRIT with ^{131}I -3F8, XRT was given up to 72 Gy to focal brain parenchymal lesions and/or up to 45 Gy CSI; for patients receiving ^{131}I -8H9 cRIT, there was no limit to prior XRT absorbed dose (in Gy). For all patients, there was at least a three week interval between XRT and cRIT. Ommaya catheter position, patency and CSF flow were evaluated in all patients pre-treatment using ^{111}In -diethylene triamine pentaacetic acid (DTPA) scintigraphy studies. Patients had baseline MRI studies of the brain and spinal cord and CSF cytology examination approximately 1 month prior to and after cRIT.

Murine monoclonal antibody 3F8 targeting disialoganglioside GD2, and 8H9 targeting B7-H3 were purified and radiolabeled at MSKCC using the iodogen method as detailed in the respective investigational new drug applications, with specific activities averaging 5 mCi/mg 3F8 or 8H9. Patients received an oral saturated solution of potassium iodide (SSKI) and liothyronine to suppress thyroid function and uptake of any free radioiodine and were premedicated with acetaminophen, lorazepam, and diphenhydramine.

cRIT injections were routinely administered in the outpatient setting. Intra-Ommaya treatments were performed as follows: For 3F8, a weekly injection of ^{131}I -3F8 (10 mCi) for a total of up to four injections. The maximum total administered activity was up to 40 mCi but with the total cRIT CSF absorbed dose not to exceed 24 Gy as projected based on pre-therapy dosimetry estimates with a 2-mCi ^{131}I -3F8 test administration). The 10-mCi therapy administrations were based on the maximum tolerated activity established in a phase I study. [4] For 8H9: 1 or 2 monthly injections ^{131}I -8H9 (10–70 mCi/injection); dosing was based on a phase I dose-escalation level at the time of patient entry or on an expanded phase II cohort treated at 50 mCi ^{131}I -8H9 per injection. The administered activity was adjusted based on CSF volume for patients less than 3 years of age (< 12 months, 50% dose reduction; 13–36 months, 33% dose reduction; > 36 months, full dose). Clinical status, vital signs and neurologic examination were monitored overnight. Repeat therapy injections were administered in the absence of grade three or four toxicity using the National Cancer Institute Common Toxicity Criteria.[5]

Upon completion of the cRIT protocol, routine MR of the brain and spine was performed approximately 1 month after the last injection, and thereafter every three months. Patients followed longer than 5 years after the completion of treatment typically had routine brain MR surveillance on an annual basis.

Dosimetry

Pre-treatment cRIT dosimetry was performed based on the 2-mCi administration of the ^{131}I - or, more recently, the ^{124}I -MoAb and serial whole body SPECT or PET, respectively. Biodistribution and activity concentrations in the craniospinal axis and radiation doses to plaques of disease and surrounding normal tissues were determined (Figure 1). The measured time-activity concentration data were corrected for physical decay of the ^{131}I or the ^{124}I to the time of administration and then fit to exponential functions as previously described.⁴ Taking into account the physical half-life of ^{131}I (the radionuclide to be used in the subsequent therapies), the resulting functions were integrated to “infinite” time, that is, to complete decay, to yield the cumulated activity concentrations (i.e. total number of decays in $\mu\text{Ci-h/mCi/gm}$) of ^{131}I in the respective source regions. ^{131}I -MoAb absorbed doses for target regions including CSF, ventricles, spinal cord, normal brain, and blood were calculated assuming complete local absorption of the ^{131}I beta radiation and ignoring the gamma radiation contribution.

Injections were followed by pharmacokinetic studies over 48 hours. Measured aliquots of CSF and blood were counted in a scintillation well counter calibrated for ^{131}I to estimate the time-dependent activity concentrations. The respective time-activity concentration data were again fit to exponential functions and integrated to yield the source region cumulated activity concentrations and the various target-region absorbed doses calculated, as previously described.[6]

Results

Ninety-six patients (58 CNS NB; 36 MB) received both CSI-XRT and cRIT, with median follow-up 41.5 months (range: 6.5–124.8 months) (Table 1). Within the MB cohort, there were 2 patients younger than 3 years at diagnosis who were treated with chemotherapy and cRIT alone, and no conventional external beam radiation therapy., and 4 patients were treated with M3 disease post CSI. For all other patients with recurrent MB, overall mean CSI absorbed dose was 28 Gy (additional boost to primary tumor mass 23.8 Gy, totaling 54–55.8 Gy); 20% had re-irradiation at a later date with a mean repeat-XRT absorbed dose of 27.5 Gy. The median CSF absorbed dose by cRIT was 18.6 (10.4–131.4 Gy). The time between CSI and cRIT varied in this patient population in that the majority was treated with cRIT at the time of MB recurrence, with a mean time from initial diagnosis to cRIT 34.5 months.

For those with CNS NB recurrence, patients were treated uniformly with a combined approach incorporating CSI followed by cRIT³, with a mean time from completion of CSI to cRIT of approximately 4 weeks. The overall mean CSI absorbed dose was 21.7 Gy (with an additional boost to parenchymal tumor masses of 10.8 Gy); 7 had re-irradiation at a later

date with focal or stereotactic XRT, mean repeat-XRT absorbed dose of 24 Gy. The mean CSF absorbed dose by cRIT was 32.1 (4.3–147.3 Gy).

Radionecrosis

Only one patient underwent resection, of a 0.6 cm hemorrhagic periventricular white matter lesion confirmed to be necrosis and granulation tissue, 2.5 years after RT. The patient presented at age 23 months with high-risk metastatic NB and was treated with multiagent chemotherapy, two tandem autologous bone marrow transplants including total-body radiation of 12 Gy, and focal RT to the primary site of 24.25 Gy. Approximately 1.5 years after initial diagnosis, the patient presented with two parenchymal CNS lesions causing symptomatic hydrocephalus. Treatment included surgical resection of the lesions, CSI 21.60 Gy and a whole brain boost of 3.6 Gy, followed by ^{131}I -8H9 cRIT (total administered activity: 64 mCi). A complete remission was achieved. Over 2.5 years later, a 0.6-cm hemorrhagic right parietal periventricular white matter lesion was noted on routine brain MRI, in the region of prior focal RT boost. Radiographically, the lesion was described as a 0.6 cm marginally enhancing lesion identified within the deep right parietal periventricular white matter, associated with a small amount of edema and containing intralesional hemorrhage supported by a blooming effect on the Bo portion of the diffusion weighted sequences. This lesion was thought to likely represents a brain metastasis, less likely to represent an occult vascular malformation or cavernous malformation given the rim like marginal enhancement. The patient was asymptomatic. The lesion was resected, with histopathology noting granulation tissue, necrosis, and hemosiderin; no tumor was seen. Although there is radiographic evidence of punctate cavernomas, no further evidence of radionecrosis has been noted on routine scans monitored over the ensuing six-plus years.

Discussion

Radionecrosis can be a devastating complication following CNS radiation. Although the exact incidence and clinical spectrum of radiation necrosis are variable, large series report an incidence of 4–5% in children with CNS tumors.[1, 7] Symptomatic patients often require surgical resection, corticosteroids, and/or hyperbaric oxygen. More recently, treatment with bevacizumab has resulted in a significant radiographic response of radionecrosis.[8] We undertook the current analysis to determine if children treated with both XRT and cRIT have an increased risk of radionecrosis.

For the initial phase II ^{131}I -3F8 study, where the risk of radionecrosis was unknown, a conservative treatment approach was followed, such that patients with a history of >72 Gy focal CNS RT or 45 Gy CSI were excluded. Further, patients with a history of prior CSI, were restricted to receive a total of four therapy injections (maximum total administered activity: 40 mCi), specifically not to exceed a total CSF cRIT absorbed dose of 24 Gy based on pre-therapy dosimetry analysis. Using these guidelines, even in a heterogeneous patient population, no patient had any evidence of radionecrosis. For the patients treated with ^{131}I -8H9, the number of cRIT, therapy injections were not limited by prior XRT dose or by cRIT dosimetry. The only occurrence of radionecrosis was in a patient with NB with an extensive radiation therapy history: total-body radiation (1200 cGy) and focal primary tumor

radiation (1225 cGy) to her left neck after initial diagnosis, and then CSI (2160 cGy) with whole brain boost (360 cGy) and cRIT (64 mCi ^{131}I -8H9) at the time of CNS relapse. The total administered activity to the brain in the area that developed necrosis was 37.20 Gy XRT, plus 64 mCi cRIT with ^{131}I -8H9. Even with this extensive XRT history, the lesion was found on a routine surveillance brain MR when the patient had no symptoms. The reported incidence of symptomatic and asymptomatic radionecrosis observed was 8.4% and 6.9%, respectively, in other patients treated with stereotactic radiosurgery for brain metastases, often correlating with the location of the lesions (superficial, deep, or central).[9] We observed no increased risk in the seven patients with NB who were treated with a subsequent focal or stereotactic boost. The antibody was conjugated with ^{131}I , with a physical half-life (8.04 days) to be commensurate with the biological half-life on the antibody in the CSF. The mean range of the β -particles emitted by ^{131}I is short (0.37mm), therefore sparing the CNS tissue from ^{131}I decays within the CSF compartment. As a consequence tumor cells within the CSF compartment will get maximum dose, yet with rapid fall off in β dose with distance from the CSF (to almost zero within 2mm). Even considering a conservative denominator for patients who have lived long enough for the full time-period risk for radionecrosis, i.e. 3 and 4 years, point estimate for radionecrosis in this cohort is approximately 2 %. The radiation dose to the CNS from the RIT is likely to be a small incremental addition above and beyond the external beam dose contribution. This study supports that notion that in pediatric patients with malignant CNS tumors, the opportunity for dose escalation with cRIT might be higher than previously appreciated.

Conclusions

The median follow-up in the current study was 41.5 months (6.5–124.8 months), within the expected time frame for a complication such as radionecrosis to be clinically demonstrable. The risk of radionecrosis in children treated with XRT and cRIT appears minimal (<1%). No neurologic deficits secondary to radionecrosis have been observed in long-term survivors treated with these combined modalities, including patients who underwent repeat-XRT. Administration of cRIT may safely proceed in patients with CSI-XRT without increasing the risk of radionecrosis. Patient-specific radiation dosimetry of cRIT (based on pre-treatment tracer studies) as well as XRT is likely important for achieving such a favorable result.

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Table 1**Patient Demographics**

Patient Characteristics–	Medulloblastoma Cohort
Medulloblastoma	N= 38 *
Age (years) initial diagnosis	6.39 Gy (0.8–33)
Males:Females	24:14
No. pts with M3 disease Rx'd with cRIT post CSI-XRT at initial diagnosis	4
No. Pts Rx'd with cRIT only	2
No. Pts alive >3 years since dx	28
No, Pts alive 3–4 years since dx	4
No. Pts alive >4 years since dx	24
Mean CSI dose	27.7 Gy (18–36.2)
Mean EBRT boost to tumor	23.8 Gy (5.4–36)
Number of patients receiving focal re-irradiation after further relapse	N=9; Mean dose 27.5 Gy (12–30.6)
Number of patients treated with stereotactic EBRT	N=5 (Dose: 12–18 Gy/1 fraction)
Mean CSF cGy/mCi 2 mCi dose	60.4 (17.4–207)
Mean CSF dose delivered by cRIT	18.6 Gy (10.38–131.43 Gy)
Mean time (months) from EBRT to cRIT	27 (1–109)
No. pts experiencing RN	1
No. pts experiencing secondary CNS malignancy	1 ⁺⁺⁺

Patient Characteristics–	Neuroblastoma Cohort
Neuroblastoma	N=58 *
Age (years) initial diagnosis	2.5 (0.17–7.3)
Males:Females	40:18
No. Pts alive >3 years since CNS dx	3
No, Pts alive 3–4 years since CNS dx	2
No. Pts alive >4 years since CNS dx	27
Mean CSI dose	21.7 Gy (10.8–36)
Mean EBRT boost to tumor	10.8 Gy (3.6–27)
Number of patients receiving focal re-irradiation after further relapse	N=7; Mean dose 24 Gy (10.8–30)
Mean CSF cGy/mCi 2 mCi dose	79.3 (6.4–312)
Mean CSF dose delivered by cRIT	32.11 Gy (4.26–147.34)
No. pts experiencing RN	1
No. pts experiencing secondary CNS malignancy	1 ^{**}

CSI- craniospinal radiation; EBRT-external beam radiotherapy; CSF-cerebrospinal fluid; cRIT-compartmental radioimmunotherapy;

⁺⁺⁺ glioblastoma mutiforme;

^{**} meningioma

^{*} dosimetry calculated for 27 pts with MB and 41 pts with CNS NB.