Hyperfractionated craniospinal re-irradiation for recurrent/progressive disseminated medulloblastoma using image-guided radiotherapy: leveraging radiobiology with technology

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Abstract Medulloblastoma, the most common primary malignant central nervous system tumor of childhood has a high propensity to spread along cerebrospinal fluid pathways. Craniospinal irradiation, therefore, remains an integral component of post-operative adjuvant treatment, even without clinicoradiological evidence of leptomeningeal metastases. Despite newer insights in molecular biology and significant advances in treatment of medulloblastoma, the prognosis of previously irradiated recurrent/progressive disease remains dismal with few long-term survivors. Leptomeningeal dissemination is the predominant pattern of relapse following curative-intent treatment that is generally not amenable to any salvage therapy including high-dose chemotherapy with stem cell rescue. Re-irradiation of the entire craniospinal axis for recurrent/progressive disseminated medulloblastoma is seldom considered feasible owing to its potential toxicity, young patient population, and uncertain efficacy. Important factors for consideration should include age at re-irradiation, prior doses of radiation, interval since first course of radiotherapy, and cumulative doses of radiotherapy. We present a case report of hyperfractionated craniospinal re-irradiation using image-guided intensity modulated radiation therapy on helical tomotherapy for progressive disseminated medulloblastoma with limited acute toxicity, encouraging early response, disease stabilization, and no significant late toxicity and discuss how leveraging

radiobiology with technology may help minimize toxicity while maintaining efficacy to optimize the therapeutic index of re-irradiation.

Keywords Craniospinal · LQ model · Medulloblastoma · Re-irradiation · Tomotherapy

Introduction

Medulloblastoma, the most common primary malignant central nervous system (CNS) tumor of childhood has a high propensity to spread along cerebrospinal fluid (CSF) pathways with leptomeningeal involvement seen in up to 30% of patients at initial diagnosis [9, 15]. Craniospinal irradiation (CSI), therefore remains an integral component of its adjuvant management even without clinicoradiological evidence of metastases [9]. Newer insights in molecular biology and significant advances in treatment have vastly improved the prognosis in this disease in recent times [14, 15]. Despite these advances, treatment failure represents a significant problem, and prognosis of previously irradiated recurrent/progressive disease remains dismal with very few long-term survivors [3, 9]. Leptomeningeal dissemination is the predominant pattern of relapse either alone or in combination with primary site recurrence that is generally not amenable to any salvage therapy including high-dose chemotherapy (HDCT) with stem cell rescue [9]. Re-irradiation of the entire craniospinal axis for recurrent/progressive disseminated medulloblastoma has seldom been considered feasible owing to its potential toxicity, young patient population, and uncertain efficacy [3].

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Purpose and methods

To report the feasibility of hyperfractionated craniospinal re-irradiation using image-guided intensity-modulated radiation therapy (IMRT) on helical tomotherapy (HT) for recurrent/progressive disseminated medulloblastoma and discuss relevant radiobiological issues. Written informed consent was obtained from the patient's caregivers for publication.

Results

Presentation A 14-year-old boy presented initially in 2005 with features of raised intracranial pressure. Magnetic resonance imaging (MRI) of the brain showed a well-defined midline vermian mass with mild contrast enhancement causing obstructive hydrocephalus (Fig. 1). He underwent a midline sub-occipital craniectomy with gross total resection of the tumor diagnosed as desmoplastic medulloblastoma on histopathology. In view of average-risk disease (no evidence of local residual tumor or leptomeningeal metastases on post-operative neuraxial imaging and negative CSF cytology), he received post-operative adjuvant radiotherapy to the craniospinal axis (30 Gy in 12 fractions to the entire spine with a single direct posterior field prescribed at skin surface, 40 Gy in 20 fractions to the whole brain with two lateral cranial portals prescribed at midplane) followed by a boost to the posterior fossa (total tumor dose of 60 Gy in 33 fractions). Subsequently, he was on regular follow-up with an annual surveillance scan that showed no evidence of disease till 2008, when a moderately enhancing intradural lesion was detected in the cauda equina from L1–L3 level, suggestive of spinal metastases. He received two cycles of systemic chemotherapy with vincristine, cisplatin, and lomustine, following which spinal MRI showed progressive leptomeningeal disease. He was then switched on another multidrug chemotherapy regimen consisting of ifosfamide, cisplatin, and etoposide. Interval imaging after three cycles showed stable disease, whereby

his chemotherapy was stopped. A repeat MRI done 3 months later showed progressive disease.

At this juncture, he was referred to us for further evaluation and salvage treatment. Neuraxial imaging showed diffusely enhancing craniospinal leptomeninges, small nodular enhancement in the right perimesencephalic cistern and a plaque-like lesion extending from the dorsal spine till the sacral spine (Fig. 2a) including nodular deposits at D1–D2 and D9–L1 levels. Associated thickening of the lumbar nerve roots was also noted. CSF was also reported as teeming with malignant small blue round cells. After discussion in the multidisciplinary neuro-oncology joint clinic, the option of HDCT with stem cell rescue was offered. However, in view of potentially poor marrow reserve due to previous history of full-dose CSI, suboptimal response to prior chemotherapy regimens and presence of grossly metastatic disease, the therapeutic index of this approach was considered to be low and unacceptable by the transplant team. In the interim, he developed progressive neurologic symptoms in the form of low backache, urinary hesitancy, and subtle weakness of the lower limbs. Progressive neurologic worsening prompted urgent initiation of curative-intent re-irradiation to the entire craniospinal axis with sequential boost to sites of gross disease using a hyperfractionated radiotherapy approach to reduce the risk of potential late toxicity.

Craniospinal re-irradiation Our process of planning and delivery of image-guided IMRT for the craniospinal axis on HT has been reported in detail previously [17]. In view of different doses delivered to the brain and spine (in the first course of radiation), a differential prescription was used for the brain and spine in the craniospinal re-irradiation plan. The planning target volume (PTV) of the brain was prescribed a dose of 30 Gy in 30 fractions (1 Gy/fraction, two fractions daily), while PTV spine received 36 Gy in 30 fractions (1.2 Gy/fraction, two fractions daily). A sequential plan to boost grossly metastatic sites delivered 15 Gy in 10 fractions (1.5 Gy/fraction, two fractions daily) to the cranial

Fig. 1 Pre-operative MRI at initial diagnosis showing a well-defined midline cerebellar vermian mass, isointense on T1-weighted images, variably hyperintense on T2-weighted images with mild enhancement that was diagnosed as desmoplastic medulloblastoma on histopathology

Fig. 2 Sagittal MRI of the spine prior to craniospinal re-irradiation (**a**) showing enhancing intradural deposits involving the cauda equina reaching till sacral spine. Response assessment imaging after image-guided hyperfractionated craniospinal re-irradiation and sequential boost showing significant regression in the size and enhancement (**b**) of the spinal leptomeningeal disease. The patient remained symptom-free for 18 months on close clinic-radiological surveillance. Repeat MRI spine showing progressive disease with multiple nodular deposits (**c**) involving the cauda equine and lumbosacral region

boost PTV in the right perimesencephalic cistern and 12 Gy in 10 fractions (1.2 Gy/fraction, two fractions daily) to the spinal boost PTVs (D1–D2 and D9–L1) for a total tumor dose of 45 and 48 Gy in 40 fractions to the brain and spine respectively. Re-irradiation of the craniospinal axis plus boost was well tolerated excepting for moderate, self-limiting hematologic toxicity (grade II thrombocytopenia and neutropenia) that did not necessitate either interruption of treatment or growth factor or transfusion support.

Response evaluation and follow-up The patient demonstrated significant neurologic recovery even during the course of re-irradiation with significant pain relief and complete resolution of urinary hesitancy and lower limb weakness. Response evaluation MRI (Fig. 2b) 6-weeks after completion of re-irradiation showed significant regression of spinal deposits as well as reduction in size and enhancement of cranial disease. Mild residual enhancement was noted in the cauda equina along with thickening and clumping of lower lumbar nerve roots. In view of the above, he was put on close clinicoradiological surveillance. He resumed his normal daily activities such as attending college, socializing, and even holidaying. Surveillance MRI scans showed further reduction in leptomeningeal enhancement. Approximately 18 months after re-irradiation, he presented with recent onset paraparesis and urinary hesitancy. Repeat MRI showed significant progression of disease with multiple nodular and plaque-like deposits over the lower dorsal and lumbosacral spine (Fig. 2c) as well as multiple small enhancing nodules in supratentorial brain. It is pertinent to

note here that even at this time, he had preserved higher mental function without any significant late neurocognitive sequelae. In view of poor marrow reserve due to two prior chemotherapy regimens and re-irradiation of craniospinal axis, he was started on oral metronomic chemotherapy with etoposide, cyclophosphamide, and celecoxib. After 1 month of oral metronomic chemotherapy, he underwent spinal decompression for progressive paraparesis. The immediate post-operative MRI showed partial excision with residual enhancing disease with diffuse thickening and clumping of lumbar nerve roots with evidence of nodular leptomeningeal enhancement. However, there was increase in the number, size, and enhancement of cranial disease suggestive of progression. He was subsequently switched to a novel oral metronomic protocol of biodifferentiating and anti-angiogenesis agents comprising celecoxib, isotretinoin, valproate, and etoposide. However, an MRI showed rapidly progressive cranial and spinal leptomeningeal disease. He finally succumbed to progressive leptomeningeal dissemination 30 months after craniospinal re-irradiation.

Discussion

Craniospinal re-irradiation may be an effective therapeutic option in patients with recurrent medulloblastoma that has been utilized sparsely due to concerns regarding potential cumulative toxicity, young patient population, and uncertain efficacy [3]. Radiation-induced late CNS injury is pathologically characterized by demyelination and vasculopathy finally leading to necrosis. The biology of late CNS toxicity represents a complex dynamic process involving several cell types (endothelial cells, oligodendrocytes, astrocytes, microglia, neurons, and neural stem cells). The two debilitating toxicities of craniospinal re-irradiation are symptomatic brain necrosis and myelitis. Other potential toxicities include myelosuppression, neurocognitive dysfunction, endocrinopathy, optic neuropathy, retinopathy, cerebrovascular accidents, and second malignancies. Although there are no effective means of treating established late CNS toxicity, it can possibly be prevented by judicious use of re-irradiation applying fundamental radiobiological principles and integrating high-precision radiotherapy technology. Prior to considering CNS re-irradiation, factors such as age; previous volume, dose, and dose per fraction; and time interval since first course of radiotherapy have to be carefully considered to guide decision making [3]. The therapeutic index of craniospinal re-irradiation also depends largely on these factors. In our patient, the factors favorable for re-irradiation included older age (>18 years at re-irradiation), slightly lower initial spinal dose (30 Gy at surface) and a long interval from the first course of radiotherapy (48 months).

Radiobiological calculations and re-irradiation tolerance
Late toxicity of fractionated radiotherapy is largely dependent on the dose per fraction and total dose (assuming similar volumes). We hypothesized that by using hyperfractionated radiotherapy, i.e., lower dose per fraction (1–1.5 Gy), two fractions per day 6–8 h apart (to allow some repair of normal tissues), we would be able to deliver adequate tumoricidal doses with reduced normal tissue toxicity at re-irradiation. Within the context of the linear–quadratic (LQ) model, we calculated the overall biological effect of prescribed doses on a given tissue using biologically effective dose (BED) and LQ equivalent dose in 2 Gy fractions (LQED₂) also called normalized total dose (NTD), for both the initial course of radiotherapy as well as at re-irradiation using an α/β value of 2 for late effects [18]. Cumulative BED was calculated by summing the BED for both courses of irradiation for whole brain, whole spine, partial brain, and partial spine volumes (Table 1). Given the debilitating toxicity that high doses of radiation can entail, CNS re-irradiation has to be approached cautiously. There is now considerable experimental and clinical evidence of substantial recovery of nervous tissue over time [2] that allows curative-intent re-irradiation for recurrent/progressive primary CNS tumors. In an overview [10] for estimating the re-irradiation tolerance of the human brain using necrosis as the endpoint, it was shown that brain necrosis occurred beyond a cumulative NTD >100 Gy. The authors also suggested that modern conformal techniques allow delivery of even higher cumulative NTD without consequent increase in the probability of normal brain necrosis. In an analysis on human spinal cord re-irradiation tolerance, Nieder et al. [12] concluded that the risk of radiation-induced myelopathy was small after cumulative BED of 135 Gy₂ when the interval between both courses of radiation was >6 months and BED of each course of radiation was

<98 Gy₂. It is now accepted that after conventionally fractionated radiotherapy (2 Gy fractions), tolerance of the spinal cord increases by at least 25%, 6 months after the initial course of radiotherapy [7]. In our patient, we were well within the re-irradiation tolerance of both the brain and spinal cord based on these estimates. The caveat is that these datasets are based on partial brain and partial spinal re-irradiation that cannot be directly extrapolated for cranio-spinal re-irradiation.

Bakst et al. [3] recently reported their institutional experience of re-irradiation in 13 patients as part of multimodality salvage strategy in recurrent medulloblastoma. Median time from initial course of radiation to re-irradiation was 57 months (range, 25–112 months). Median dose of re-irradiation was 30 Gy (range, 19.8–45 Gy), with a median fraction size of 1.5 Gy (range, 1.0–1.8 Gy). Median cumulative dose was 84 Gy (range 65–98.4 Gy). IMRT was used for over half the patients at re-irradiation. Subsites of re-irradiation were posterior fossa ($n=5$), supratentorial/whole brain ($n=4$), spine ($n=3$), and craniospinal ($n=1$). For the entire cohort, the 5-year Kaplan–Meier estimates of progression-free and overall survival since first recurrence were 48% and 65%, respectively. With a median follow-up of 30 months, re-irradiation was well tolerated, without significant acute effects, treatment-related deaths, or second malignancy and only one case of asymptomatic in-field radiation necrosis at 39 months.

In a study of prognostic factors in 46 children with recurrent/progressive medulloblastoma, Bouffet et al. [4] identified recurrence limited to a single site; use of radiotherapy at progression; and good response to salvage therapy as significant factors for postprogression survival. In another similar analysis [6] involving 46 children with recurrent disease, improved survival was associated with recurrence limited to primary site alone; initial therapy with

Table 1 Prescription dose, dose per fraction (fx), biologically effective dose (BED), normalized total dose in 2-Gy fractions (NTD) for both courses of radiotherapy (initial and re-irradiation 48 months apart)

Volume of radiation	Prescription dose	Dose/fx (Gy)	BED ₂ (Gy)	NTD (Gy)
Whole brain _{Initial}	40 Gy/20fx	2.0	80	40
Posterior fossa boost _{Initial}	20 Gy/13fx	1.55	35.5	17.75
*Whole spine _{Initial}	30 Gy/12fx	2.5	67.5	33.75
	24 Gy/12 fx	2.0	48	24
Whole brain _{Re-irradiation}	30 Gy/30fx	1.0	45	22.5
Whole spine _{Re-irradiation}	36 Gy/30fx	1.2	57.6	28.8
Brain boost _{Re-irradiation}	15 Gy/10fx	1.5	26.25	13.125
Spine boost _{Re-irradiation}	12 Gy/10fx	1.2	19.2	9.6
Cumulative whole brain dose			125	62.5
Cumulative dose to partial brain			186.75	93.375
Cumulative whole spine dose			125.1	62.55
*Cumulative whole spine dose			105.6	52.8
Cumulative dose to partial spine			144.3	72.15
Cumulative dose to partial spine ^a			124.8	62.4

^aThe first course of spinal irradiation was prescribed as 2.5 Gy per fraction at the surface, resulting in delivery of around 2 Gy per fraction to the spinal canal (assuming the cord to be at 5 cm from surface). Thus the actual cumulative BED to partial volume of spine was likely to be between 125 and 145 Gy₂

co-operative group regimen; and treatment with radiotherapy at first progression. In a slightly younger cohort of 38 patients (median age=5 years), Rutkowski et al. [5] reported local versus meningeal relapse and circumscribed meningeal relapse versus diffuse meningeal involvement being associated with better overall postprogression survival. They also perceived that delaying radiotherapy may have contributed to relapse.

Since most patients would have received several active chemotherapeutic agents (vincristine, cisplatin/carboplatin, cyclophosphamide/ifosfamide, nitosoureas, etoposide) at initial diagnosis in conjunction with radiotherapy, the choice of drugs at relapse remains controversial. Recently, temozolomide has shown good efficacy in recurrent pediatric brain particularly medulloblastoma [1, 11], either alone or in combination with other agents. Systemic chemotherapy may be an essential component of salvage, but occasionally it may be difficult to achieve sufficient concentration of cytotoxic drugs in the CNS due to the presence of blood–brain barrier. In such scenario, a potentially effective yet underutilized salvage treatment is intrathecal chemotherapy [20] through ventriculo-lumbar perfusion that achieves requisite drug concentration in the ventricular system and spinal subarachnoid space to exert appropriate therapeutic effect in leptomeningeal dissemination.

There is conflicting data on the role of HDCT and stem cell rescue for patients with previously irradiated recurrent medulloblastoma. Finlay et al. [19] enrolled 25 patients achieving minimal disease state on a prospective salvage protocol of carboplatin, thiotepa, and etoposide followed by

autologous stem cell rescue. The Kaplan–Meier estimate of median overall survival was 26.8 months, while the 10-year overall survival was 24%. Five of these patients were also treated with re-irradiation at relapse either focal ($n=3$) or craniospinal ($n=2$), that showed a trend towards better event-free survival ($p=0.07$). European investigators, however, either reported very limited benefit using similar strategy. In a series [8] of 17 patients relapsing after prior standard therapy, significant responses were obtained in vast majority, but additional relapses occurred in all but one patient with a median remission duration of 16 months; 15 patients died of further disease progression, one of pneumonia, leaving the lone long-term survivor who had excision of a single spinal metastasis and re-irradiation. A co-operative group study [13] enrolled 40 patients with relapsed medulloblastoma and treated them initially with cyclophosphamide with surgery or local radiotherapy as appropriate. Patients achieving complete or near complete remission ($n=22$) proceeded to two sequential courses of HDCT with stem cell rescue. With a median follow-up of 7.4 years, 37 patients died due to tumor progression ($n=35$), respiratory failure ($n=1$), or post-treatment myelodysplasia ($n=1$), with an estimated 3- and 5-year survival of 22% and 8%, respectively. The five subgroups of patients that are likely to have a consistently better prognosis are: primary site recurrence alone; single site recurrence; chemotherapy or radiotherapy-naïve patients; good response to salvage therapy; and minimal residual disease prior to salvage HDCT.

HT has emerged as a novel approach to radiation treatment wherein a linear accelerator mounted on a ring gantry

Fig. 3 Dose-wash of helical tomotherapy-based re-irradiation of the craniospinal axis in axial (a), coronal (b), and sagittal (c) sections showing delivery of 30 Gy (green) to the PTV brain and 36 Gy (red) to PTV spine. The 50% dose wash (light blue) is also depicted to show modest spillage. Dose wash of sequential boost (d) to focal nodular deposits in the brain, upper dorsal and lower dorsolumbar spine

continuously rotates around the patient to deliver radiation in helical mode [17]. The large and complex target volume poses technical challenges in conventional CSI, necessitating couch rotation and field junction(s) with inherent uncertainty in abutment dosimetry, poor homogeneity across spinal fields, and suboptimal organ-at-risk (OAR) sparing. HT obviates these and seems to be ideally suited for the planning and delivery of CSI with excellent high-dose conformality, OAR sparing, and homogeneity (Fig. 3). In addition, it allows in-room volumetric verification for precise and accurate patient positioning on a daily basis. In the final analysis, although we could not cure our patient, hyperfractionated craniospinal re-irradiation and sequential boost provided immediate and sustained neurological improvement with minimal acute and late toxicity resulting in excellent quality of life for over 18 months till further disease progression. Given the perceived advantages, there is potential for using high-technology radiotherapy for selected patients for sustained and effective palliation [16].

Conclusion

The prognosis of previously irradiated recurrent/progressive medulloblastoma remains dismal with very few long-term survivors. Craniospinal re-irradiation may be an effective therapeutic option for leptomeningeal dissemination at relapse in carefully selected patients. Important factors for consideration include age at re-irradiation, prior doses of radiation, interval since first course of radiotherapy, and cumulative doses of radiotherapy. Leveraging radiobiology with technology may help minimize toxicity while maintaining efficacy to optimize the therapeutic index of re-irradiation.

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