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ORIGINAL RESEARCH

Maintaining Survival While Improving Quality of Life: An Advanced Practitioner–Led Pilot Feasibility Study to Reduce Radiation Dose in Children With Brain Tumors

JENNIFER L. RAYBIN,[1] PhD, RN, CPNP, ANDREW DONSON,[1] NICHOLAS K. FOREMAN,[1] MRCP, RAJEEV VIBHAKAR,[1] MD, MICHAEL H. HANDLER,[1] MD, and ARTHUR K. LIU,[2] MD, PhD

From [1]Children's Hospital Colorado, University of Colorado Anschutz Medical Campus, Aurora, Colorado; [2]Radiation Oncology, University of Colorado, Aurora, Colorado

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Jennifer L. Raybin, PhD, RN, CPNP, 13123 E. 16th Avenue, Aurora, CO 80045
E-mail: jennifer.raybin@cuanschutz.edu

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Abstract

Purpose: Oncology advanced practitioners (APs) are on the front line in treating adverse effects. Among children with brain tumors, treatments such as craniospinal irradiation (CSI) cause neurocognitive injury, endocrinopathies, and ototoxicity. High-dose CSI with concurrent chemotherapy allows high-risk embryonal tumors (non-anaplastic) good survival (70%), but significant distressing effects are commonly treated by APs in multidisciplinary long-term follow-up. The aim of this study was to test feasibility of reducing radiation dose with an AP-led protocol. **Methods:** An interdisciplinary team developed this pilot study with the primary outcome of fewer than two deaths in 10 patients (80% survival). Secondary outcomes were feasibility of an AP-led treatment protocol and acute/late effects of treatment. The AP held a pioneering role as principal investigator of a tumor treatment study. Exclusion criteria included age less than 3 years and anaplasia. The CSI was reduced from 36 to 24 Gy. All other treatment was standard. **Results:** Survival rate exceeded the primary outcome threshold (88%); the accrual rate (80%) and follow-up neurocognitive testing rate (75%) were acceptable. Eight children ages 3 to 19 years (M = 8) with tumors of varied molecular subtyping were enrolled. The single death occurred 2.5 years from diagnosis of multiorgan failure (without evidence of tumor). The mean survival is 11 years, with two college and one graduate degrees. Acute and late effects were decreased compared with the higher-dose CSI. **Conclusion:** APs who treat cancer adverse effects can also conduct clinical prospective studies to maintain survival rates and improve quality-of-life-outcomes.

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Advanced practitioners (APs) are integral clinicians in the care of patients experiencing adverse effects of cancer treatments. They are also on the front lines in the daily discussions of prognosis between patients and interdisciplinary oncology teams. An opportunity exists for APs to improve both survival rates and late effect outcomes through collaboration on clinical research (Braun-Inglis et al., 2022). Advanced practitioners in pediatric oncology have demonstrated the feasibility of conducting supportive care protocols (Montgomery et al., 2021). Here, we present outcomes from an AP-led treatment study to maintain survival rates but reduce adverse effects among children with historically poor prognosis brain tumors.

Embryonal brain and spine tumors were historically classified as medulloblastomas and primitive neuroectodermal tumors (PNET). These small, round, blue cell tumors occur in the infratentorial space (medulloblastoma) or in the supratentorial area (pineoblastoma or PNET). These classifications have become outdated with the evolution of molecular subtyping. High-risk embryonal tumors of the central nervous system are those that are metastatic within the brain or the spinal cord. Other risk factors for poor prognosis include embryonal tumors that are supratentorial or have anaplasia/large cell histology. Anaplasia and large cell histology are associated with the lowest survival rates for this type of tumor.

Radiation therapy to the tumor site has been effective to improve survival. Focused radiation delivery to the primary tumor site is referred to as the "boost." Because these tumors have microscopic metastases, radiation therapy at a lower dose to the whole brain and spinal cord (craniospinal irradiation [CSI]) has further improved survival. The use of CSI has allowed these children to be cured, but at a cost to quality of life. Many survivors of these tumors who received CSI at a young age are unable to live independently or maintain intimate relationships. Advanced practitioners who clinically care for these patients both during the acute chemotherapy/radiation treatment and during survivorship are challenged with speaking to patients and parents who struggle with the choice of reduced survival vs. long-term neurologic injury.

In children with standard-risk embryonal brain tumors (age > 3 years old, no metastatic disease, residual disease < 1.5 cm^2, and non-anaplastic/large cell histology), the 5-year overall survival (OS) is greater than 80% (Packer et al., 2006). Children with high-risk disease have worse outcomes, even with more intensive therapy that typically includes higher doses of CSI of 36 gray (Gy; Esbenshade et al., 2016; Gajjar et al., 2006; Kortmann et al., 2000; Tarbell et al., 2013; Zeltzer et al., 1999). The Children's Oncology Group (COG) study 99701 examined the use of high-dose radiation (36 Gy CSI) with concurrent daily carboplatin as a radiation sensitizer in high-risk embryonal tumors (Jakacki et al., 2015; Jakacki et al., 2012). The study showed promising results, with a 5-year progression-free survival of 75% for high-risk patients. However, 36 Gy of CSI was known to result in worse late effects such as increased cognitive deficits (Merchant et al., 2014; Moxon-Emre et al., 2014) and poor quality of life as an adult (Ribi et al., 2005).

The most recent study by COG (ACNS0332) was a randomized trial treating children with high-risk medulloblastoma with 36 Gy CSI. The experimental arm received concurrent carboplatin during radiation. Results revealed that event-free survival improved by 19% at 5 years (73.2% with concurrent carboplatin vs. 53.7% without carboplatin) in children in the molecular subtype high-risk group 3 medulloblastoma (Leary et al., 2021). Reported toxicities in the carboplatin arm were worse during the radiation phase, but equivalent during the maintenance phase of treatment. Neurocognitive outcomes showed a mean intelligence quotient (IQ) score of 91 with a mean processing speed more than a full standard deviation below the mean. The carboplatin (experimental) arm did not have a significant difference in neurocognitive outcome (Leary et al., 2021).

Clinically, our multidisciplinary team included neuro-oncology, radiation oncology, endocrinology, neuropsychology, neurosurgery, rehabilitation, radiology, ophthalmology, audiology, and nutrition. The interdisciplinary roles included physicians, nurses, social workers, APs, dieticians, physical therapists, occupational therapists, and speech therapists. In our monthly clinic, we provided care for children with these tumors during

treatment and afterwards in survivorship. Standard-of-care tools for monitoring adverse effects of treatment included serum levels of hormones, endocrinological history and physical exams, ophthalmological exams, audiology, and neurocognitive testing. A dedicated neuropsychologist evaluated patients with a standard neurocognitive battery of tests such as the Wechsler IQ scale. Within each of these subspecialties, thresholds for treatment or intervention have been established and followed in standardized survivorship protocol roadmaps through COG. For instance, high-frequency hearing loss is diagnosed when a child has a decrease of 30 decibels (dB) or more at the frequency of 4,000 hertz (Hz).

All team members involved in this clinic voiced challenges in providing optimal care to survivors who were unable to live independently. Parents and caregivers questioned the quality-of-life outcomes for their child, verbalized anxiety about their child's future, and some stated decisional regret about high-dose radiation treatment. We therefore sought to use a pilot study feasibility design to examine the use of a lower dose of CSI (24 Gy) with concurrent carboplatin. We excluded patients in the extremely high-risk category of anaplastic tumors because the decision to reduce treatment intensity would be more likely to reduce survival and therefore would be unacceptable to patients, parents, and providers. The goal was to maintain similar disease outcomes with lower neurocognitive toxicity to allow for better quality of life for survivors. We also wanted to include more disciplines in clinical research and therefore assigned the neuro-oncology AP as the principal investigator (PI) with the other team members as co-investigators.

METHODS

The primary goal of this pilot study was to determine survival in a limited group of patients with high-risk embryonal tumors who received reduced-dose CSI (24 Gy) with concurrent carboplatin. Secondary aims included feasibility of an AP-led treatment protocol and evaluation of acute/late effects of therapy. The institutional review board (IRB) approved the pilot study with the accrual goal of 10 children. The research team was asked to provide additional evidence to the IRB that the AP as a PI would be well-supported by the physician co-investigators and that the AP had previous independent research experience in supportive care trials.

Eligibility criteria included: (1) age between 3 and 25 years old, (2) classical or desmoplastic embryonal histology in the posterior fossa with metastatic disease; or nonmetastatic supratentorial embryonal tumors, and (3) expected survival of greater than 6 weeks. Patients with anaplastic histology were excluded. Written informed consent/assent from each subject or their authorized representative was obtained prior to enrollment. Initial evaluation included standard clinical exam, laboratory studies, MRI of the brain before and after surgery, MRI of the spine, lumbar puncture, and audiogram.

Tumors were diagnosed by standard pathology. Retrospective evaluation of molecular subtyping was completed because it was not yet standard practice during the years of study enrollment. Where available, tumor tissue was subject to methylation-based diagnostic classification. DNA was extracted from tumor samples and applied to Illumina EPIC 850K methylation arrays. Resulting IDAT files were uploaded to molecularneuropathology.org/mnp for molecular subgroups/subtypes assignment.

The protocol therapy included CSI 24 Gy (23.4 Gy in 1.8 Gy per fraction) with a primary tumor boost of 32.4 Gy in 1.8 Gy per fraction (total dose to primary tumor bed of 55.8 Gy). Supratentorial metastatic disease received a boost of 32.4 Gy (total dose 55.8 Gy), and spinal metastatic disease received a boost of 27 Gy (total 50.4 Gy). Carboplatin was given daily 1 to 4 hours prior to each fraction of radiation at 35 mg/m^2 IV over 15 to 20 minutes for 6 weeks (total of 30 doses). Weekly vincristine was given at 1.5 mg/m^2 for 6 weeks. Following chemoradiation, patients received the standard adjuvant chemotherapy (cisplatin, CCNU, cyclophosphamide, vincristine) based on COG study 9961 (Packer et al., 2006).

Conservative study endpoints for safety included two deaths from disease or any therapy-related death. Acute toxicity (hematologic and nonhematologic effects according to the National Cancer Institute's Common Terminology Criteria for Adverse Events) was recorded during the 6 weeks of

chemoradiation. Expected late effects in patients who have received whole-brain radiation were recorded with routine follow-up. These included hormonal deficiencies related to panhypopituitarism, high-frequency hearing loss, presence of cataracts, and a decrease in neurocognition measured by IQ testing. Routine follow-up was conducted according to the standard of care with MRIs and late effect testing in our multidisciplinary clinic every 3 months for 1 year, every 6 months for the subsequent 2 years, and yearly after that.

RESULTS

Participant descriptions and toxicities are summarized in Table 1. The study was open for 8 years and enrolled eight participants (80% of accrual goal). Given the slow accrual, it was closed prior to reaching the goal of 10 patients. Five-year progression-free survival (PFS) was 85%. Overall survival was 88%, and there were no deaths from disease.

The eight participants included four with a diagnosis of medulloblastoma and four with supratentorial tumors. The medulloblastoma subtypes were two group 4, one group 3, and one not otherwise specified by standard pathology. The supratentorial subtypes were three pineoblastomas and one cerebral neuroblastoma. All the medulloblastomas had metastatic disease: two were staged M3 with spinal metastases, and two were staged M1 with tumor cells in the cerebrospinal fluid. All four supratentorial embryonal tumors were included given the poor outlook for these tumors. All participants were able to complete concurrent chemoradiation as outlined in the protocol and all had expected hematologic toxicity. Three of the participants had nonhematologic grade 3 toxicities during the chemoradiation.

One patient relapsed 2 years after diagnosis and currently has no evidence of disease after salvage therapy. One patient died without any evidence of tumor recurrence 2.5 years off therapy, not thought to be related to treatment. The diagnoses at this patient's death included enterococcal infection, multisystem organ failure, and acute respiratory distress syndrome. Of note, this subject had a normal complete blood count and differential upon admission with the infection.

Expected late effects of cranial radiation were assessed. Six patients had endocrine dysfunction and needed hormone replacement therapy. Six patients were diagnosed with high-frequency hearing loss (> 30 dB at ≥ 4,000 Hz). Two patients had cataracts. Four participants had cognitive evaluations at diagnosis and 2 years later (Table 1). Two had declines in IQ scores, one had an increase, and one was unchanged (Figure 1). Four patients have now graduated from high school, two from college, and one from graduate school.

The AP as PI maintained the protocol requirements including ensuring patients completed the long-term follow-up standard-of-care visits. Rate of neurocognitive testing completion at 2 years was 75%. The participants are currently at a median time of follow-up since diagnosis of 11 years (range 7–14 years).

DISCUSSION

We hypothesized that APs can actively collaborate in clinical research to explore if there are some children with high-risk embryonal tumors that can be treated less aggressively but still maintain good disease outcomes. Thus, our AP-led pilot study aimed to evaluate if reducing the dose of CSI for high-risk embryonal tumors could retain similar survival rates but decrease toxicity. Although the study had a small sample size, we successfully showed 5-year survival over 80%. The one death was thought to be related to overwhelming infection despite a normal blood count and occurred remotely from protocol treatment without evidence of tumor recurrence. The AP as PI successfully conducted the study with completion of long-term follow-up evaluations including 80% of overall neurocognitive follow-up, which compares favorably to the historical rate (Moxon-Emre et al., 2014).

Outcomes for children with high-risk embryonal CNS tumors have been poor. To improve those outcomes, there have been multiple attempts at intensifying therapy. This has included the use of higher-dose CSI, typically 36 Gy or higher, and additional chemotherapy. COG 99701 used a regimen that included 36 Gy CSI and daily carboplatin and weekly vincristine followed by adjuvant chemotherapy (Jakacki et al., 2015; Jakacki et al., 2012). For children without anaplasia, 5-year PFS and OS were 75% and 83%, respectively. POG 9631 was another cooperative group study that added

Table 1. Summary of Participants and Toxicities

Age (yr)	Pathology	Methylation score	Metastatic stage	Tumor location	Heme toxicities (grade 3/4)	Nonheme toxicities (grade 3/4)	Hormonal (replacement)	High-frequency hearing loss	Cataracts	IQ at baseline	IQ at 2 yr	Relapse	Death	Yr from dx
6	MB[a]	No match	3	PF/spine	Leukopenia, lymphopenia, neutrophenia	None	GH, thyroid	Yes	Yes	122	92	Yes	No	12
12	MB GP3[b]	0.94	1	PF/CSF	Lymphopenia, leukopenia, neutropenia	None	None	Yes	No	84	87	No	Yes	2.5 at death
4	MB GP4[b]	1.00	1	PF/CSF	Leukopenia, lymphopenia, neutropenia, thrombocytopenia	Hydrocephalus	GH, thyroid	Yes	No	–	80	No	No	8.5
8	MB, GP4[b]	0.99	3	PF/spine	Leukopenia, neutropenia, lymphopenia, thrombocytopenia	Headache	GH, thyroid, testosterone	Yes	No	99	90	No	No	14
19	Pineoblastoma[a]	0.97	0	Pineal	Lymphopenia, leukopenia, neutropenia	None	Thyroid, testosterone	No	No	111	127	No	No	13
6	Pineoblastoma[a]	N/D	0	Pineal	Lymphopenia, leukopenia, neutropenia, thrombocytopenia	Vomiting, leg pain, jaw pain	None	Yes	No	96	–	No	No	7
3	Pineoblastoma[b]	0.92	0	Pineal	Thrombocytopenia, neutropenia, lymphopenia	None	GH, thyroid	Yes	No	–	105	No	No	13
7	Cerebral neuroblastoma[a]	No match	0	R temp	Leukopenia, lymphopenia, neutropenia	None	Thyroid	No	Yes	–	–	No	No	13

Note. High-frequency hearing loss defined as > 30 dB at ≥ 4,000 Hz. MG = medulloblastoma; GP = group; N/D = not done; PF = posterior fossa; CSF = cerebrospinal fluid; GH = growth hormone.
[a]Diagnosis by standard pathology.
[b]Diagnosis by methylation array.

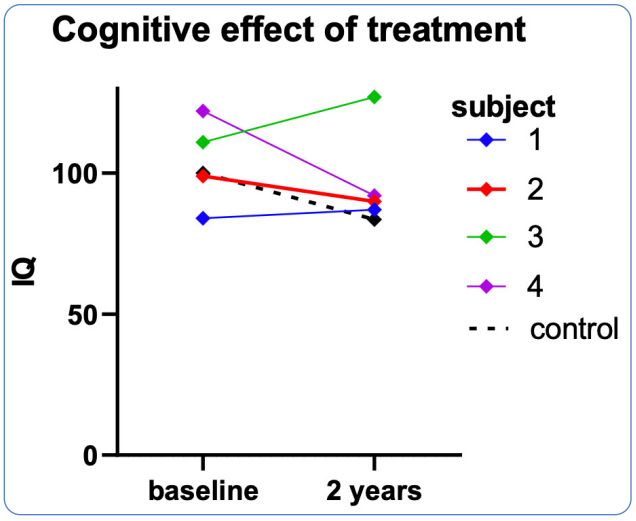

Figure 1. Cognitive effect of treatment compared with historical norm. The rate of change of IQ score in the 4 patients who had testing at baseline and 2 years were similar or better than the published rate of decrease in IQ scores in children with high-risk embryonal tumors (Mulhern et al., 2005).

etoposide to high-dose CSI followed by adjuvant chemotherapy for children with high-risk medulloblastoma (Esbenshade et al., 2016). For the entire cohort, 5-year PFS and OS were 70% and 77%, respectively. Data regarding anaplasia were not included. In both studies, therapy was considered tolerable in the short term. In our study of eight subjects, we had one relapse and one death unrelated to disease, which compares favorably with COG 99701 (Jakacki et al., 2015; Jakacki et al., 2012). Finally, the recently published COG study ACNS0332 for children with high-risk medulloblastoma randomized participants to 36 Gy CSI with or without concurrent carboplatin. For all participants, the 5-year PFS was 62.9% and OS was 73.4% (Leary et al., 2021). Although we had a small sample size, our study again maintained similar survival rates to the most recent study but with a reduced dose of radiation.

In terms of molecular subtyping, our treatment approach seemed successful for group 4 medulloblastomas and the single group 3 medulloblastoma. Of note, in the subsequent ACNS0332 trial for patients with high-risk medulloblastoma, the addition of carboplatin was seen to significantly benefit children with group 3 medulloblastoma when treated with 36 Gy (Leary et al., 2021). The excellent outcome for the three patients with pineoblastoma in our sample is also notable.

While the disease control with high-dose radiation regimes of 36 Gy is good, there is significant therapy-related late toxicity. A CSI dose of 36 Gy results in cognitive deficits and poor reported quality of life, especially when a child is treated at a younger age (Mulhern et al., 2005). Our outcomes revealed that reducing the CSI dose to 24 Gy while intensifying therapy with concurrent daily carboplatin resulted in tolerable acute toxicity (primarily hematologic). Endocrinopathies, hearing loss, and cataracts were common, but not worse than has been reported in patients who received 36 Gy CSI (Jakacki et al., 2012).

Regarding neurocognitive outcomes, the patients in our cohort have attained better educational achievement than the decrease of 8 IQ points per year that has been reported with higher-dose CSI (Figure 1; Mulhern et al., 2005). Additionally, three of our patients have achieved higher education degrees, which differs from historical reports. Older age when radiation was delivered may affect this outcome (the patient who completed graduate school received radiation as an older adolescent), although age was not found to significantly affect neurocognitive outcomes in the historical comparison (Mulhern et al., 2005). Also, the recent national trial using 36 Gy CSI appears to have a worse outcome for mean IQ (91) compared to our patients (97) at about 2 years from diagnosis. That study also confirmed that the addition of carboplatin did not worsen IQ outcomes between groups (Leary et al., 2021). Although our numbers are small and timepoints are difficult to compare, the neurocognitive effects appear to be at least equivalent to those reported in ACNS0332, and not worse (Figure 1).

In support of the concept behind this pilot study, large cooperative groups are investigating how to decrease adverse effects of cancer treatment in pediatrics. Children's Oncology Group is pursuing supportive care trials to improve quality-of-life outcomes among children with brain tumors. In neuro-oncology, a trial of modafinil for treatment-related fatigue successfully reached accrual goals and neurocognitive testing timepoints, perhaps related to the engagement of APs involved in the trial (Sung et al., 2013). A new study

based on success in adults (Brown et al., 2020) has opened to examine the role of memantine as a neurocognitive protectant for children with brain tumors receiving cranial radiation. Conceivably, this is another opportunity for APs to champion clinical research to investigate supportive care interventions for children with brain tumors. Pediatric APs can explore opportunities to be local coinvestigators for national multisite studies or PIs of institutional pilot feasibility studies.

Confirming our positive result for the feasibility of an AP-led trial, authors of a recent nationwide survey of 408 oncology APs found that 80% reported feeling comfortable with clinical research and trials, but 73% wanted to be more involved and 90% felt that oncology APs should play a role in clinical research (Braun-Inglis et al., 2022). Other examples of AP-led trials include the recent publication of a prospective clinical trial in symptom assessment in advanced pediatric cancer. Displaying the strengths of an AP-focused research study, these authors were the first to report successful data collection in the last 12 weeks of life in children with cancer (Montgomery et al., 2021). However, authors of both studies suggest that challenges continue to exist in infrastructure, protected time, and research education for APs in oncology. In our study, the collaboration between interdisciplinary team members highlighted the strengths of the AP in symptom management and coordination, with the scientific support of the physicians.

LIMITATIONS

Our results are limited by the lack of full molecular subtyping due to the rapid evolution of diagnostic techniques during the study period. Because we wanted to establish equivalent survival before exposing children to a treatment with potentially reduced efficacy, we limited our accrual goal to 10 participants. Larger numbers are warranted to examine statistically significant outcomes.

CONCLUSIONS

Children with brain tumors benefit from AP-led clinical research trials that promote interdisciplinary collaboration to improve quality-of-life outcomes. Newer molecular classifications could be used to further define this lower-risk cohort (Cho et al., 2011; Northcott et al., 2011). For example, if a child has a better prognosis by molecular classification, the risk of reducing therapy may be less, and therefore quality of life could be prioritized. Due to these positive findings, lower-dose CSI could be validated in a larger study to continue the work toward the goal of improving survival while decreasing late neurocognitive effects in children with high-risk disease. Advanced practitioners are a group of providers who are readily engaged in symptom management and interested in the control of cancer toxicities. Therefore, APs have the potential to significantly contribute to the clinical investigation of reducing adverse effects while maintaining survival rates among patients with cancer.

Disclosure

The authors have no conflicts of interest to disclose. Trial registration number: ClinicalTrials.gov record 06-1151, "Concurrent Carboplatin and Reduced Dose Craniospinal Radiation for Medulloblastoma and Primitive Neuroectodermal Tumor (PNET)."

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