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Reduced-dose Radiation Therapy to the Primary Site is Effective for High-risk Neuroblastoma: Results from a Prospective Trial

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Abstract

Purpose: For patients with high-risk neuroblastoma (HR-NB), a dose of 21 Gy to the primary tumor site after gross total resection (GTR) provides excellent local control. However, no clinical trial has specifically evaluated the optimal dose of radiation therapy (RT), and RT-related long-term toxicities are of increasing concern. We sought to assess local control, survival outcomes, and toxicity after a reduction in dose to the primary site from 21 Gy to 18 Gy.

Methods and Materials: After induction chemotherapy and GTR, patients with HR-NB were enrolled and treated on a RT dose-reduction prospective trial with 18 Gy hyperfractionated RT given in twice-daily fractions of 1.5 Gy each.

Results: The 25 study subjects were 1.6–9.5 (median 4.3) years old at enrollment and included 23 (92%) with stage 4 and two (8%) with *MYCN*-amplified stage 3 disease. Eleven (44%) were in complete remission (CR), and 14 (56%) had persistence of osteomedullary disease postinduction. Three patients (12%) received proton therapy, while the rest received intensity-modulated photon therapy. After a follow-up of 1.8–4.2 (median 3.5) years from initiation of RT, no failures occurred within the RT field; three patients had marginal recurrences. The respective 3-year progression-free and overall survival rates were 54.5% and 90.9% for patients in first CR, and 42.9% and 76.2% for patients not in metastatic CR. Acute toxicity was negligible.

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Conflicts of interest: N.K. Cheung reports receiving commercial research grants from Y-mabs Therapeutics and Abpro-Labs Inc.; holding ownership interest/equity in Y-Mabs Therapeutics Inc., holding ownership interest/equity in Abpro-Labs, and owning stock options in Eureka Therapeutics. N.K. Cheung is the inventor and owner of issued patents licensed by MSK to Ymabs Therapeutics, Biotech Pharmacon, and Abpro-labs. Hu3F8 and 8H9 were licensed by MSKCC to Y-mabs therapeutics. Both MSK and N.K. Cheung have financial interest in Y-mabs. N.K. Cheung is an advisory boardmember for Abpro-Labs and Eureka Therapeutics. S. Modak and S.L. Wolden report personal fees at Y-mabs Therapeutics. D.L Casey, B.H. Kushner, E.M. Basu, S.S. Roberts, and M.P. LaQuaglia have no disclosures to report.

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Conclusion: Reduced-dose RT with 18 Gy did not compromise local control or survival outcomes in our cohort of patients with HR-NB after GTR. These findings support assessing further RT dose reduction and validation on a larger, multi-institutional trial.

SUMMARY

We developed a prospective radiation dose-reduction protocol for patients with high-risk neuroblastoma, with the goal of maintaining disease control while reducing late morbidity. We found that dose reduction from 21 Gy to 18 Gy after gross total resection did not compromise local control or survival outcomes in our cohort of 25 patients with high-risk neuroblastoma.

INTRODUCTION

Treatment of high-risk neuroblastoma (HR-NB) involves dose-intensive induction chemotherapy, surgical resection, local radiation therapy (RT), anti-GD2 immunotherapy and differentiation therapy. This aggressive multi-modality program has improved progression-free survival (PFS) and overall survival (OS) for HR-NB, but entails major acute and long-term toxicities.^{1,2} As regards RT, a dose of ~21 Gy to the primary site has been widely used as a part of consolidation and is associated with excellent local control rates of >90% after gross total resection (GTR) of the primary tumor.³⁻⁵ Although this RT dosing predisposes to late toxicities including diabetes mellitus and growth abnormalities,⁶⁻⁸ RT dose-reduction has not been tested in neuroblastoma, unlike has been done in other pediatric tumors.^{9,10} To help fill this gap, we developed a prospective dose-reduction protocol at Memorial Sloan Kettering (MSK) for HR-NB from 21 Gy to 18 Gy, with the goal of maintaining disease control while decreasing long-term morbidity. The primary objective of the protocol was to assess local control and patterns of failure after a reduction in RT dose, with the secondary goals of assessing survival outcomes and toxicity.

PATIENTS AND METHODS

HR-NB patients who underwent GTR were eligible to enroll on the RT dose-reduction prospective trial, MSK protocol 14-186 ([ClinicalTrials.gov NCT02245997](https://clinicaltrials.gov/ct2/show/study/NCT02245997)). HR-NB was defined as stage 4 disease diagnosed at age >18 months or *MYCN*-amplified stage 3 or 4 at any age. Exclusion criteria included prior RT to the primary tumor bed and gross residual soft tissue NB (as determined by post-operative imaging of the primary site). Toxicity was scored by the Common Terminology Criteria for Adverse Events Version 4.0 (CTCAEv4). Informed written consents for this trial were obtained according to institutional review board rules.

Protocol RT comprised 18 Gy in 12 fractions given twice-daily on weekdays. Both intensity-modulated RT with photons and proton therapy were allowed. The clinical target volume (CTV) consisted of the post-induction chemotherapy, pre-operative tumor volume, and the planning target volume consisted of an additional 5mm expansion on the CTV in order to account for spatial uncertainties in patient positioning and treatment delivery.

To assess local control (LC) and PFS, patients underwent ^{123}I -meta-iodobenzylguanidine scan and computed tomographic and/or magnetic resonance imaging of the primary site, plus bone marrow evaluations, at least every 3 months for 2 years.

Statistical analysis

The primary objective was to assess LC rates following reduced-dose RT to the primary site, defined as no relapse within the RT field. Secondary endpoints included PFS, OS, and toxicity. With a 1-year expected LC rate of 95% after standard dose RT (21 Gy) at our institution,³ we enrolled 25 patients to be treated with reduced dose RT at 18 Gy, with a decision rule that, if at least 23 patients were local failure free 1 year from RT, then 18 Gy would be deemed acceptable (this was equivalent to a 1-year LC sample proportion of 92%). This decision rule has a type 1 error rate of 0.032 when the true 1-year LC rate is 75%, and a power of 0.873 when the true 1-year LC rate is 95%. For the secondary objectives, PFS was calculated as the time from initiation of systemic therapy to disease progression (including local and/or distant relapse), and OS as the time from initiation of therapy to death from any cause. The Kaplan-Meier method was used for the analysis of LC and survival outcomes, and survival curves among subgroups of patients were compared with the Mantel log-rank test.

RESULTS

From 9/2014-4/2017, 25 patients enrolled (Table 1). The median age at time of study enrollment was 4.3 years (range, 1.6-9.4). Twenty-three of 25 patients (92%) had stage 4 HR-NB, and 8 (32%) had *MYCN*-amplified disease. After induction therapy, 11 patients (44%) were in complete remission (CR) by international criteria.¹¹ Three patients (12%) received proton therapy, while the rest received intensity-modulated photon therapy. Additional post-induction treatment included anti-GD2 antibody therapy with either murine-3F8 (n=20)^{12,13} or humanized-3F8 (n=5).¹⁴ Most patients (80%) received RT in between cycles 1 and 2 of antibody therapy. After the completion of antibody therapy, 12 patients received a bivalent anti-NB vaccine.¹⁵

After 1.8-4.2 (median 3.5) years from initiation of RT, no local failures occurred. Three patients experienced a marginal failure, defined as a soft tissue failure near but completely outside of the RT field in a location that received 0 Gy as per dosimetric review, at 1.1, 1.1, and 2.4 years from RT (Figure 1). The respective PFS and OS rates at 3 years were 54.5% and 90.9% for patients in first CR, and 42.9% and 76.2% for patients not in metastatic CR (Figure 2).

All acute toxicities were grade 1, including nausea (n=16), fatigue (n=10), dermatitis (n=3), diarrhea (n=3), and vomiting (n=2). Late toxicities were minimal at this early follow up time point, with focal nodular hyperplasia of the liver seen in 2 patients, and short stature in 1 patient.

DISCUSSION

With a LC rate of 100% after RT dose-reduction on this prospective trial, 18 Gy was a sufficient dose post-GTR for patients in our cohort. Although there were 3 marginal failures, all occurred superior to the RT field in locations that did not receive any radiation dose as per dosimetric review. As such, these failures were likely secondary to volumetric constraints rather than dose insufficiency, as 18 Gy successfully controlled disease wherever it was delivered. To address such failures in the future, generous margins should be given in the superior and inferior directions to cover all at-risk nodal regions. PFS and OS were similar on our study to a large cohort of HR-NB patients treated with 21 Gy after GTR at our institution.¹⁶ As a result of these findings showing excellent LC and survival outcomes, 18 Gy was deemed an acceptable dose level on our protocol, and we are now prospectively studying 15 Gy in a step-wise fashion.

A reduction in RT dose of 3-6 Gy is small in magnitude, but highly promising for sparing late effects. The RT fields used for HR-NB are generally extensive (Figure 1). Impairment of linear growth, which results from the irradiation of vertebral bodies that are inevitably included in the RT field, is both age- and dose-dependent. The steepest part of the dose-response curve for growth impairment is from 15-21 Gy. This observation highlights the importance of confirming the efficacy of 18 Gy because the favorable result supports exploring the aforementioned further dose reduction to 15 Gy. This lower dosing promises a significant decrease in musculoskeletal toxicity.¹⁷ Developing diabetes mellitus after abdominal RT is also a dose-dependent toxicity, with a relative risk of 6.8 after 10-19.9 Gy to the tail of the pancreas versus 11.4 with 20-29 Gy.⁶ Additionally, the 30-year cumulative incidence of second cancers in neuroblastoma survivors is 5.8%.¹⁸ Like diabetes mellitus and growth impairment, the risk of radiation-induced cancers (with the exception of thyroid cancer) increases linearly with dose.^{19,20} Besides RT dose-reduction, proton therapy also holds promise in sparing late morbidity due to the stopping power of protons that allows for minimal dose to normal tissue beyond the target.²¹ However, even with proton therapy, the ipsilateral kidney dose is often difficult to spare, which further supports the use of lower doses regardless of RT modality.

Laboratory findings and analysis of the limited literature available led to our adopting hyperfractionated 21 Gy as standard to assure LC for HR-NB.¹ *In vitro* studies in the 1980's demonstrated the limited DNA repair capacity and exquisite radiosensitivity of HR-NB cell lines.^{22,23} The surviving fraction after low doses of radiation (2 Gy) was similar to that of cell lines of other highly radiosensitive malignancies, such as lymphoma and myeloma, which exhibit this phenotype both in culture and in patients.²⁴ The implication was that low radiation doses may suffice for disease control in HR-NB, especially in the adjuvant setting. Preclinical studies also suggested that hyperfractionation is less toxic to normal tissues, and hyperfractionation allows for completion of RT within much shorter time periods than daily fractionation. This in turn facilitates the administration and scheduling of RT between cycles of immunotherapy, which is our current practice.

The biologically effective dose (BED) of 18 Gy given in twice daily fractions of 1.5 Gy (as utilized on our protocol) is 20.7 Gy, which is similar to the BED of 21.2 Gy seen with 18 Gy

given in 1.8 Gy daily fractions (α/β ratio of 10). Given this similarity, we expect dose reduction to 18 Gy utilizing daily fractionation to result in comparable outcomes, although this must be validated on a larger, multi-institution study. Importantly, given the logistical inability to perform twice daily anesthesia and hyperfractionated treatment at other institutions, replication of our results with daily fractionation is imperative for broader applicability.

To date, no preclinical or prospective clinical studies have specifically evaluated the optimal RT dose needed as a part of consolidative therapy for HR-NB. Data from the Children's Cancer Study Group CCG-3891 trial for HR-NB suggested that 20 Gy was superior to 10 Gy for macroscopic gross disease.²⁵ However, CCG-3891 was designed to assess the role of transplant rather than radiation dose, and only patients with gross residual disease after surgery received external-beam RT supplemental to total body irradiation. Such patients represent a distinct subgroup of HR-NB patients who likely require higher doses of RT (36 Gy) than patients like those in this cohort who undergo GTR.²⁶ Single-institutional series^{4,5,16} showed good LC with 20-24 Gy and helped make doses of ~21 Gy standard for HR-NB after GTR. Yet unlike other pediatric tumors such as Wilms tumor,⁹ Hodgkin lymphoma,¹⁰ medulloblastoma,²⁷ and rhabdomyosarcoma,²⁸ in which RT dose-reduction has been tested in prospective trials, dose-reduction in HR-NB has not been previously explored. Although late morbidity has decreased in the Childhood Cancer Survivor Study cohort for several malignancies, long-term toxicities have become an ever more serious concern among survivors of HR-NB, attributed to an increase in therapeutic intensity.² It is imperative in pediatric tumors to find the minimal dose necessary of any intensive therapy in order to minimize late morbidity in long-term survivors. For HR-NB specifically, with its radiosensitivity, excellent LC after GTR and ~21 Gy, and recent addition of targeted immunotherapies that have improved survival without significant additional toxicity,^{12,28} it is the appropriate time to consider treatment de-escalation such as RT dose-reduction.

As novel targeted approaches and immunotherapy for HR-NB continue to mature, it will be important to evaluate whether other intensive and toxic non-targeted therapies can be limited or even omitted without compromising prognosis. For example, since 2003, HR-NB patients at MSK have received anti-GD2 immunotherapy using murine-3F8 or humanized-3F8 but have not undergone autologous stem-cell transplantation unless this toxic treatment was previously administered at the referring institution. Importantly, multi-factorial analyses of a large clinical experience revealed no difference in survival with the omission of transplant when patients receive anti-GD2 immunotherapy.²⁹ All patients in the current cohort received anti-GD2 immunotherapy, with at least one cycle preceding protocol RT in 24 of the 25 study patients. This timing contrasts with practice elsewhere, including the Children's Oncology Group protocol ANBL0032 in which immunotherapy was given after completion of RT.³⁰ The optimal sequencing of RT and immunotherapy has not been explored in neuroblastoma, but it is plausible that concurrent delivery could enhance local and systemic tumor control. In addition, high-throughput next-generation sequencing has allowed for genomically-guided prognostication and treatment strategies. Identification of a molecularly-characterized, favorable subgroup of patients with HR-NB that may respond to even lower doses of RT or no RT at all is an area of future exploration.

In conclusion, this study provides preliminary evidence that 18 Gy may be a sufficient dose of RT to help prevent local failure after GTR, although this must be tested in a larger cohort with daily fractionation. Our next step is to evaluate whether further dose-reduction to 15 Gy on our protocol will provide a similarly excellent rate of LC and survival. Importantly, our encouraging results must be validated in a larger, multi-institutional trial before reduced-dose RT is accepted as standard of care.

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Figure 1.

Imaging of the three patients with marginal failures showing the extent of tumor at diagnosis, the radiation therapy (RT) fields, and the location of the marginal failure outside of the RT field.

Figure 2.

a) Progression-free survival and b) overall survival from start of therapy by response to chemotherapy (CR=complete response, PR/SD=partial response/stable disease)

Table 1.

Patient characteristics (N=25)

Characteristic	No. (range)	%
Gender		
Male	17	68
Female	8	32
Age at diagnosis, years		
Median (range)	3.7 (1.1-9.0)	
Age at enrollment, years		
Median (range)	4.3 (1.6-9.4)	
Stage		
3	2	8
4	23	92
MYCN status		
MYCN non-amplified	17	68
MYCN amplified	8	32
Site of primary tumor		
Adrenal	17	68
Central abdominal compartment	6	24
Mediastinum	2	8
Tumor size, cm		
Median (range)	9.6 (2.0-16.0)	
Prior induction chemotherapy		44
COG	11	44
XXX	11	12
Rapid COJEC	3	
Response to induction chemotherapy		
Complete remission	11	44
Persistent disease	14	56

Abbreviations: COG, Children's Oncology Group; xxx, xxx; COJEC, cisplatin vincristine carboplatin etoposide cyclophosphamide.