Published in final edited form as:

J Neurooncol. 2010 May ; 97(3): 409–418. doi:10.1007/s11060-009-0038-7.

Compartmental Intrathecal Radioimmunotherapy: Results for Treatment for Metastatic CNS Neuroblastoma

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Abstract

Innovation in the management of brain metastases is needed. We evaluated the addition of compartmental intrathecal antibody-based radioimmunotherapy (cRIT) in patients with recurrent metastatic central nervous system (CNS) neuroblastoma following surgery, craniospinal irradiation, and chemotherapy. 21 patients treated for recurrent neuroblastoma metastatic to the CNS received a cRIT-containing salvage regimen incorporating intrathecal ^{131}I -monoclonal antibodies (MoAbs) targeting GD2 or B7H3 following surgery and radiation. Most patients also received outpatient craniospinal irradiation, 3F8/GMCSF immunotherapy, 13-cis-retinoic acid and oral temozolomide for systemic control. Seventeen of 21 cRIT-salvage patients are alive 7-74

months (median 33) since CNS relapse, with all 17 remaining free of CNS neuroblastoma. One patient died of infection at 22 months with no evidence of disease at autopsy, and one of lung and bone marrow metastases at 15 months, and one of progressive bone marrow disease at 30 months. The cRIT-salvage regimen was well tolerated, notable for myelosuppression minimized by stem cell support (n=5), and biochemical hypothyroidism (n=5). One patient with a 7-year history of metastatic neuroblastoma is in remission from MLL-associated secondary leukemia. This is significantly improved to published results with non-cRIT based where relapsed CNS NB has a median time to death of approximately 6 months. The cRIT-salvage regimen for CNS metastases was well tolerated by young patients, despite their prior history of intensive cytotoxic therapies. It has the potential to increase survival with better than expected quality of life.

Keywords

Neuroblastoma; Radioimmunotherapy; CNS metastases; intrathecal

Introduction

Neuroblastoma (NB) is the most common extracranial solid tumor in children. Recurrent metastatic NB is difficult to cure, particularly in patients with central nervous system (CNS) disease.[1] The CNS has emerged as a sanctuary site leading to relapse. Among large series, the incidence of leptomeningeal (LM) or CNS parenchymal disease in relapsed patients is 6-8%. [2, 3] CNS relapses have been almost always fatal [1-3] –hence the need for innovative treatments. Compartmental radioimmunotherapy (cRIT) using radioiodinated monoclonal antibodies (MoAbs) administered intrathecally results in a favorable cerebrospinal fluid (CSF) to blood activity concentrations and radiation dose ratios and may be useful in the treatment of LM disease.[4-6] For example, cRIT using ¹³¹I-labeled murine anti-tenascin MoAbs in patients with malignant glioma was feasible, well tolerated and improved survival.[7-9]

A phase I study at Memorial Sloan-Kettering Cancer Center (MSKCC) demonstrated the feasibility of cRIT for patients with GD2-expressing LM neoplasms using the anti-GD2 murine MoAb 3F8 labeled with ¹³¹I.[10] Another murine MoAb, 8H9, is specific for 4Ig-B7H3, a 58 kD surface immunomodulatory glycoprotein that inhibits natural killer cells and T cells. The B7-H3 protein is distributed on the cell membrane of a broad spectrum of pediatric and adult solid tumors, preferentially expressed on tumors as compared to normal human tissues.[11] When radiolabeled with ¹³¹I, 8H9 can deliver therapeutic doses of radiation to solid tumors and suppress tumor cell growth in established xenografts.[12] We now report the survival of patients with relapsed CNS NB treated with a cRIT-based salvage regimen targeting minimal residual disease.

Methods

Staging was carried out according to the International Neuroblastoma Staging System.[13] CNS NB was defined as LM disease or metastatic deposits in the CNS parenchyma excluding skull bone-based metastases. Disease was confirmed pathologically in 20 patients, and radiographically in 1 patient with numerous enhancing masses.

Overall Treatment Plan

The overall salvage regimen in 17 patients from July 2003 through March 2009 is summarized in table 1. Parenchymal CNS disease was immediately resected when possible, with concurrent placement of an intraventricular Ommaya catheter to deliver intrathecal therapy. Craniospinal irradiation (1080-2160 cGy) was delivered in twice daily fractions

over a 3 week period, with a boost to parenchymal masses (up to 3000 cGy total) when possible. Craniospinal irradiation was delivered in the outpatient setting in conjunction with a course of irinotecan followed by a course of irinotecan-temozolomide $\pm$ carboplatin.[14] The resulting myelosuppression was reversed by infusion of previously collected peripheral blood stem cells when necessary. Consolidation with cRIT then began (see below). After completing the cRIT protocol, outpatient maintenance systemic therapy consisted of immunotherapy using intravenous 3F8 plus granulocyte-macrophage colony-stimulating factor (GM-CSF) as previously described,[15, 16] oral 13-cis-retinoic acid,[17] and oral temozolomide.[18] This study was approved by MSKCC IRB, and informed written consents for all treatments were obtained from guardians prior to treatment after they understood the potential side-effects of each agent and the possibility of unforeseen toxicities.

cRIT treatment—Patients were enrolled into a protocol testing cRIT, ^{131}I -3F8 (n=3, NCT00445965), or ^{131}I -8H9 (n=18, NCT00089245) for individuals with high-risk metastatic CNS tumors. The decision to use 3F8 or 8H9 was dependent on protocol opening/timing (intrathecal ^{131}I -3F8 was the first available antibody) and systemic disease status (intrathecal ^{131}I -3F8 allowed for two cycles of systemic chemotherapy between injections). Homogenous reactivity to 3F8 [19] and 8H9 [11] on neuroblastoma tumors has previously been demonstrated and was not required at study entry. Eligible patients had no rapidly deteriorating neurologic examination or obstructive hydrocephalus, had 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 $< 2 \text{ mg/dl}$. Ommaya catheter position, patency and CSF flow were evaluated by pre-treatment 111-Indium diethylene triamine pentaacetic acid (DTPA) studies. Patients had baseline magnetic resonance imaging (MRI) studies of the brain and spinal cord and CSF cytology examination approximately 1 month prior to and after cRIT.

MoAbs 3F8 and 8H9 were purified and radiolabeled at MSKCC using iodogen [20] according to specifications detailed in the respective investigational new drug applications, averaging 5 mCi/mg 3F8 or 8H9. Patients received an oral saturated solution of potassium iodide and liothyronine to suppress thyroid function and were premedicated with acetaminophen, lorazepam and diphenhydramine.

Intra-Ommaya treatment comprised: a) an injection of ^{131}I -3F8 (10 mCi) every 2-3 weeks for a total of four injections (total dose 40 mCi) based on the MTD established on a phase I study [10] or b) 1 or 2 monthly injections ^{131}I -8H9 (10-60 mCi/injection). Dosing was based on the treatment plan on the phase II study (3F8) or the phase I dose escalation level (8H9) at the time of patient entry. Dose adjustments based on CSF volume were made 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 injections were administered in the absence of grade 3 or 4 toxicity using the National Cancer Institute Common Toxicity Criteria.[21]

Upon completion of the cRIT protocol, CNS and systemic disease status was assessed approximately every 3 months by CT of the primary site, MRI brain and spine, ^{123}I -meta-iodobenzylguanidine (MIBG) scans, multiple bone marrow aspirations and biopsies, CSF cytology and urine catecholamine analyses.

Dosimetry—Pre-treatment dosimetry was obtained by 2 mCi of ^{131}I - or more recently ^{124}I -MoAbs, followed by serial whole body Single Photon Emission Computerized Tomography (SPECT) or Positron Emission Tomography (PET) scans, respectively. Distribution and activity concentrations of radioactivity in the craniospinal axis, and

radiation doses to plaques of disease and surrounding normal tissues were determined (Figure 1). ^{131}I -MoAb radiation doses for target organs including CSF, ventricles, spinal cord, normal brain and blood were based on the assumption of complete local absorption of the ^{131}I beta radiation.

Injections were followed by pharmacokinetic studies in CSF and blood. Measured aliquots were counted to estimate the time-dependent activity concentrations. The respective time-activity data were fit to exponential functions, which were integrated to yield the decayed area under the curves (AUCs), representing the cumulative activity concentrations in the blood and CSF as previously described.[10]

Results

Tables 2 and 3 present the clinical characteristics and demographics of the 21 patients who received this salvage regimen of surgery, craniospinal irradiation, chemotherapy, and intra-Ommaya ^{131}I -MoAb-therapy. Only 13 (62%) of 21 patients had complete surgical resection of CNS lesions, with two having bilateral craniotomies. In the remaining 8 patients, complete surgical resection was not possible because of tumor location, multiple parenchymal metastases or overt LM disease. Of the 21 patients, 16 received craniospinal irradiation dose 21 Gy, 3 more recent patients received 18 Gy, and prior radiation therapy limited the dose in 2 patients (#2 and #8).

Toxicity

Craniospinal irradiation was associated with transient and self-limited somnolence syndrome. Manageable acute toxicities from chemotherapy included self-limited diarrhea following irinotecan and myelosuppression requiring stem cell support after chemotherapy in five patients. Following cRIT injections, self-limited fever, nausea and headache were seen after ^{131}I -3F8, or after ^{131}I -8H9 administration, transient grade 1 creatinine elevation, and grade 1 and 3 transient elevated serum transaminase. No significant myelosuppression was seen following cRIT injections of ^{131}I -3F8 or ^{131}I -8H9 injections at dose levels 10-30 mCi. Self-limited myelosuppression was observed for ^{131}I -8H9 injections 40 mCi.

Two years after cRIT, one patient developed idiopathic thrombocytopenic purpura which resolved by 6 months. Five patients remain on oral thyroid hormone replacement for biochemical hypothyroidism attributed to treatment. Supplemental growth hormone administration for short stature has been administered to one patient. Cataract removal was performed in one patient 2 years after detection of CNS disease. In another patient, MLL-associated secondary leukemia emerged 3 years after cRIT, 4 years after dura relapse and 7 years from the initial NB diagnosis; successful treatment with an allogeneic bone marrow transplant followed.

Among the seven patients tested with formal neurocognitive evaluations, no unexpected deficits were noted. 17 children attending primary school are mainstreamed in regular classes, although two patients are receiving additional early intervention services (patients #3 and 7).

Survival

17 of the 21 patients remain alive 7-74 (median 33) months from the time of CNS NB diagnosis (Figure 2), all with no evidence of CNS disease. The longest survivor (patient #1), having had refractory bone marrow NB after myeloablative chemotherapy and then LM spread, is now 6.5 years in continuous CNS and systemic complete remission (Figure 3). Three deaths occurred from non-CNS events. One patient (#5) died of pulmonary infection 23 months after the detection of LM NB that had initially progressed following craniospinal

irradiation; she achieved a long-standing remission of disease with resolution of NB on spine MR and CSF cytology following ^{131}I -8H9; no NB in the CNS or otherwise was detected at autopsy. One patient (# 14) died of refractory lung and bone marrow NB 15 months after the CNS event and another died of progressive bone marrow disease 30 months after the CNS event. Only one patient (# 9) progressed in the CNS, 14 months after the initial CNS event and 2 months after his third marrow relapse. He died of both progressive CNS and systemic disease 35 months after the CNS event. As extended survival was observed in patients treated with both ^{131}I -3F8 and escalating doses of ^{131}I -8H9 on the phase I study, there was no clear therapeutic response favoring one cRIT mAb over the other.

Discussion

Metastatic NB remains one of the most difficult malignancies to cure. The CNS is a sanctuary site for NB. Current treatments for CNS relapses are inadequate, carrying a high morbidity and mortality rate. Few advances have affected the clinical outcome for such patients. Upfront treatment strategies including thiotepa-based myeloablative regimens for newly-diagnosed patients do not adequately treat the CNS.[22] Novel agents that may detect and treat microscopic disease may improve patient survival. We reviewed 21 patients treated at MSKCC since 2003 for relapsed NB involving the CNS treated uniformly with an approach aimed at eradicating bulky and microscopic residual disease in the CNS, as well as minimal residual systemic disease that may herald further relapses. Neurosurgical intervention served to decrease edema, control hemorrhage, and remove bulky tumor prior to starting radiation therapy. Although craniospinal irradiation required daily anesthesia for this very young patient population, this treatment was well tolerated in the outpatient setting, even with concurrent irinotecan. Stem cell rescue was necessary for those patients in whom bone marrow reserve was marginal at the time of CNS relapse.

This is the first time intrathecal radiolabeled MoAbs have been incorporated into curative treatment strategies for patients with CNS NB. At the current doses, intraventricular administration of ^{131}I -3F8 or ^{131}I -8H9 is associated with manageable, acute side effects including transient headache, nausea, fever, and vomiting. We have established that a tumoricidal dose to the CSF can be delivered by a single injection, with levels to the blood and bone marrow below clinical toxicity. For a GD2-positive free floating tumor cell suspension, as in the case of LM disease, the enhancement in dose to the cells binding 3F8 can be as great as 77%.[23] If one extrapolates the radiation dose to tumor cells based on their preferential binding (>10:1) to these MoAbs, a substantial therapeutic window between effective tumor cell ablation and the dose received to normal brain and blood could be achieved.

The extended survival of this patient population is encouraging given the rapidly fatal nature of CNS relapse – no survivors among 11 patients, median time to death of 6.6 months - in our previously published experience before initiation of the current treatment program.[2] This poor survival among patients with CNS NB has been noted in other large series. Among 23 patients with recurrent metastatic CNS NB reviewed by Matthay et al.,[3] despite treatment, 20 patients died <9.8 months and 22 of 23 by 13 months after the time of CNS disease detection. Shortened survival was most notable for patients with LM disease, 0.9-6 months[3, 23].

We recognize that this cohort of patients is limited by selection in that even in the cRIT – era, rapid deterioration and death may occur in some patients within days or weeks, usually from widespread refractory systemic or LM disease, precluding treatment initiation or completion. In contrast to patients whose CNS disease occurs in the setting of rapidly

progressing systemic NB, CNS disease as an isolated relapse appears to be readily controllable and possibly curable with the proposed regimen, even when multiple parenchymal nodules at the time of relapse are detected. It is difficult to ascertain the impact of any individual treatment modality in this encouraging salvage regimen. Surgical debulking of parenchymal masses was possible in 62% of patients. Temozolomide - irinotecan chemotherapy was primarily used to control systemic NB, as previously reported, [14] but is advantageous in this setting because of penetrance across the blood-brain-barrier.

The integral role of craniospinal irradiation is also acknowledged. However, while it likely aids in disease control, external beam radiotherapy to the craniospinal axis and to sites of resected or unresected visible disease has been part of unsuccessful treatment programs previously reported.[2, 3] Because of the young patient age and success of 2100 cGy for microscopic residual disease for the primary site,[24] no patient received 2340 cGy or 3600 cGy craniospinal irradiation, the dose typically administered to patients with medulloblastoma in attempt to sterilize the thecal space. Indeed, among our 17 survivors after cRIT-salvage, two were treated with a lower dose of radiation therapy because of prior relapses and radiation exposure (1080 cGy and 1350 cGy), and 3 at 1800 cGy. One patient had progressive nodular enhancement of spinal cord leptomeninges post radiation (2160 cGy). Treatment response was noted after serial injections of ^{131}I -8H9 therapy. As the target cGy delivered by cRIT is increased, we believe it is safe to reduce the dose delivered by conventional external beam radiation therapy, and are now delivering 1800 cGy to current patients. We also note the encouraging preclinical data demonstrating the enhanced therapeutic effect of combination external beam radiation therapy and cRIT, compared to that observed with either therapy alone.[25, 26] This combination of reduced-dose craniospinal irradiation aimed at controlling bulk parenchymal and nodular LM disease and cRIT targeting micrometastatic NB, may well be contributing to the prolonged survival seen in our patient cohort.

Several questions require focused study in the immediate future. What is the lower limit of craniospinal irradiation that can be administered with cRIT? What is the minimal total dose CSF cGy delivered by cRIT that still achieves sterilization of the thecal space? Is there an advantage of 3F8, whose acute and long term toxicity have been well characterized, over 8H9? If the external beam dose of craniospinal irradiation is reduced, in all likelihood, cRIT with 8H9 would be more advantageous than 3F8 given its higher mCi/injection. Alternatively, cRIT with 3F8 is not associated with myelosuppression in patients with poor bone marrow reserve. The use of alternative radioisotopes, such as alpha-emitting ^{225}Ac -8H9 under preclinical investigation, may further improve the efficacy of cRIT with MoABs. As ^{124}I -8H9 PET/CT provides higher resolution and contrast images than SPECT with ^{131}I -8H9 for distribution, targeting and dosimetry, ^{124}I -8H9/PET appears to be a promising tool that may aid in the treatment planning for radioimmunotherapy trials for CNS malignancies. This may allow for patient-specific dosimetry on future phase II studies, where a specific total CSF cGy is desirable.[27]

Our results support the importance of timely administration of multi-modality therapy including surgery and sterilization of the craniospinal axis with combined external beam radiotherapy and cRIT with ^{131}I -3F8 or ^{131}I -8H9. Eliminating the sanctuary site for NB in the CNS has resulted in both long-term local-regional and systemic disease control.

We demonstrate that a multi-modality treatment program centered on radiolabeled MoAb to target radiation to CNS tumors using CSF as a conduit appears to improve the survival of patients with relapsed CNS NB, even in the presence of overt LM disease. The modest and manageable side effects of the cRIT are also noteworthy. CNS prophylaxis may be possible if the NB patient population at high risk for CNS relapse can be identified at the time of

diagnosis. Such a combined multi-modality approach to improve survival may be applicable to other solid tumors metastasizing to the CNS.

Acknowledgments

We wish to thank the Cyclotron-Radiochemistry Core of MSKCC and Yiauchung Sheh for production and supply of the I-124.

This study was supported in part by the FDA-KK-01A2, CA89935, CA89936, CA106450, CA117076, FD003089, PO1 CA033049, Robert Steel Foundation, Katie's Find A Cure Fund, Pediatric Cancer Foundation, Aubrey Fund, Hope Street Kids, Major Fund, Leptomeningeal Research Fund, the MSKCC Experimental Therapeutics Center and the Ludwig Center for Cancer Immunotherapy.

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Figure 1. ^{124}I -8H9 Positron Emission Tomography Scan obtained 48 hours post Intra-Ommaya injection demonstrating distribution throughout the thecal space and activity within leptomeningeal deposits.

Figure 2. Kaplan-Meier curve demonstrating overall survival in months from CNS disease detection for 17 patients treated with current cRIT-based treatment plan

Figure 3.

A) Relapsed metastatic NB in a patient who remains progression-free, now 68+ months since detection of CNS disease (B). This patient had leptomeningeal disease and a subtotal resection, followed by craniospinal irradiation and cRIT.

Table 1
General cRIT- based treatment plan for patients with relapsed CNS NB

Time	Intervention
Day 0	Resection of CNS disease when possible; Ommaya catheter placement
Day 7	Irinotecan 50 mg/m ² /dose IV daily ×5
Day 14	Craniospinal irradiation 1080- 2160 cGy/boost 2560-3000 cGy
Week 7	Irinotecan 50 mg/m ² /dose IV daily ×5
	Temozolamide 250 mg/m ² /dose daily ×5
	Carboplatin 500 mg/m ² /dose daily ×2 (only if systemic NB present) Stem cell rescue *
Week 14	Serial injections of intra-Ommaya ¹³¹ I-MoAbs
Week 30	GMCSF/IV 3F8 every 3-4 weeks (4 cycles)
Weeks 40-104	Oral Cis-retinoic acid 160 mg/m ² day × 14 days (6 cycles) alternating with Oral temozolomide 75 mg/m ² /day × 42 days (5 cycles)

* if needed; MoAbs- monoclonal antibodies; GMCSF-granulocyte macrophage colony stimulating factor;

3F8 – monoclonal anti-GD2 antibody

Table 2
Clinical History and Demographics of 21 Patients with Relapsed CNS NB Treated with cRIT - based Salvage Regimen

Pt	Age Dx(mon)/Gender	MYCN, LDH	Sites of Initial Disease	Treatment at Dx	Type of Relapse	Time to CNS Relapse (mon)	Treatment of CNS relapse	Dosimetry (cGy/mCi)	Total RIT CSF dose (cGy)	Disease Status	Overall Survival (mon since CNSevent)
1	46, M	NA, 1090	L adr, B, BM, orbits	CAV × 3, P/VP × 2 thio/ABMT, S, RT, 3F8, CRA	2 lesions, LM;	22	Subtotal S, CSI 21 Gy, Irino/tmz, 131-I-3F8, 131-I-8H9	23.6-33.8 (3F8), 20-37 (8H9)	1397	CR	74
2	4, M	A, 12796	R adr, pleural, liver, orbits, B, BM	CAV × 3, P/VP × 2 thio/ABMT, S, RT, 3F8, CRA	2 nd relapse, 1 right temporal lesion	30	Subtotal S, CSI 1080 cGy, Irino/tmz, 131-I-8H9	36.5-79.5	1038	CR	63; MLL-associated t-AML developed 3.5 years after CNS event treated successfully
3	24, F	A	R RP, B, BM,	CAV × 3, P/VP × 2, thio/ABMT, S, RT, 3F8, CRA	1 left parietal	20	S, CSI 21 Gy, Irino/tmz, 131-I-8H9	20.8-47	1423	CR	53
4	16, M	A, 1132	R, adr, B, BM supraclav LN	CAV × 3, P/VP × 2 S, RT, 3F8, CRA	1 left temporal;	14	S, CSI 21 Gy, Irino/tmz, 131-I-8H9	55-65	1230	CR	53
5	73, F	A, 2330	R, adr, L, paraspinal, liver, B, BM	CAV × 4, P/VP × 2, S, RT, 3F8, CRA	2 nd relapse- BM, LM brain, spinal cord, CSF pos	19	CSI 21 Gy, carbo, irino/tmz, 131-I-8H9	43.2-49.5	2364	Died of infection 24 months after CNS dx; no NB at autopsy	
6	19, F	A, 3165	R, adr, B, BM, orbits	CAV X4, P/VP x2, carbo-VP-melphalan/ABMT) S, CRA	3 lesions: frontal and temporal;	14	S (1 of 3 lesions), CSI 21 Gy, irino/tmz, 131-I-8H9	24-38	2594	CR	52
7	23, F	NA, 751	Cervical, BM	PVP × 1, carbo-VP, CAV × 2, Tandem ABMT (TBI/melphalan and cytox-carbo), CRA	2 nd relapse; 2 lesions: cerebellar, right frontal	18	S, CSI 21 Gy, irino/tmz, 131-I-8H9	18-35	1688	CR	47
8	48, F	NA	L, adr, mediastinal,	PVP x, ifos-VP x1, CAV x1, CV	1 left temporal	20	S, CSI 1350 cGy,	23-28	1001	CR	43

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			supraclavicular, BM	x3, Tandem ABMT (carbo-VP, and thio-cytos), CRA			irino/tmz, 131-I-3F8				
9	24, M	NA	R, paraspinal, B, BM	CAV x3, PVP x3, carbo-VP-melphalan/ABMT, CRA	2 nd relapse-2 lesions-left frontal, right frontal	35	S, CSI 21 Gy, irino/tmz, 131-I-8H9	24-25	1857	BM relapse 10 mon after CNS event, f/b CNS PD 14 mon later; DOD 35 mon after CNS event	
10	29, F	NA, 1616	L adr, skull, BM	CAV x3, PVP x3, carbo-VP-melphalan/ABMT, CRA	Right frontal, abd disease	16	S, CSI 21 Gy, carbo/irino/tmz, 131-I-3F8	28.5	1354	CR	41
11	56, M	NA, 1712	R adr, BM, B	5 cycles high dose chemo, MIBG/ABMT, cyclo/topo, 3F8, CTV x 2, CRA	Right frontal, + Bony lesion	37	S, CSI 21 Gy, irino, irino/tmz, 131-I-3F8	23.5	823	Relapse in rib lesion at time of CNS event being treated; AWD	33
12	37, M	NA, 1161	L adr, B, BM	carbo-PV-C/VP/V, MIBG/ABMT, 3F8, CRA	2 lesions: Left and right temporal	21	S (1 of 2 lesions), CSI 21 Gy, irino, Irino/tmz carbo/irino/tmz/cyt/VP 131-I-8H9	27.1	1471	Relapse in BM 9 mon after CNS event; DOD 30 mon after CNS event	
13	36, M	A	L adr, B, BM	CAV x3, PVP x3, carbo-VP-melphalan/ABMT, CRA	Right frontal	32	S, CSI 21 Gy, irino/tmz, 131-I-8H9	71.5	3309	CR	28
14	38, M	A, 2700	R adr, B, BM	Cyclo/topo, CAV x2, PVP x1, carbo-VP-melphalan-MIBG/ABMT, Hu 14.18-IL2, irino/tmz x2	2 lesions- Right temporal and tectal; refractory systemic NB	19	S (1 of 2 lesions), CSI 21 Gy, irino, irino/tmz/carbo, 131-I-8H9	35-44	2135	Persistent bone and BM NB; DOD 15 mon after CNS event	
15	9, M	NA, 1336	L adr, testes, penis, BM	Observed -had spontaneous regression until St 4 NB age 2.5 yrs, then treated	2 nd relapse, 6 parenchymal masses	35	CSI 21 Gy, irino, irino-tmz, 131-I-8H9	147	8820	CR	20

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				with CAV ×3, PVP ×2, 3F8							
16	30, F	NA	R adr, liver, BM	CAV ×3, PVP ×2, CTV ×2, 3F8	L middle cranial fossa with herniation	9	S, CSI 21 Gy, irino, irino-tmz, 131-I-8H9	17.2	1788	CR	14
17	18, F	A	R adr, thoracic, lumbar and sacral masses, right mandible, BM	carbo-P/V-C/VP/V, CTV ×2, 3F8	Cerebellar mass	11	S, CSI 21 Gy, irino, irino-tmz, 131-I-8H9	23.8	2384	CR	12
18	19, M	A	L supraclavicular node, BM, cortical bone, malignant pleural effusion	Cyclo/topo ×2, Cisplatin/Etoposide ×2, CAV ×2, ABMT, RT, 3F8	R LM cerebellopontine angle	10	Subtotal resection, Irino-tmz ×2, CSI 21 Gy, 131-I-8H9	*	*	CR	10
19	5, F	A	R adr, R rib lesion	Carbo/Etoposide, CAV ×3, Cisplatin/Etoposide ×2, S, ABMT	cerebellar mass	18	S, CSI 18 Gy, Irino-tmz, 131-I-8H9	*	*	CR	10
20	40, M	NA	L adr, B, BM	PVP ×2, CAV ×3, ifos/VP, irino-carbo-tmz, S, RT, 3F8/Glucan, CRA	L anterolateral frontal lobe	19	S, CSI 18 Gy, Irino-tmz, 131-I-8H9	*	*	CR	9
21	22, F	A	L adr, B	carbo-P/V-C/VP/V, S, CTV, RT, 3F8, CRA	R superior temporal gyrus	31	S, CSI 18 Gy, Irino, Irino-tmz, 131-I-8H9	*	*	CR	7

Abbreviations: 3F8, anti-GD2 monoclonal antibody 3F8 treatment; 8H9, monoclonal antibody 3F8 treatment; adr, adrenal; ABMT, myeloablative treatment with autologous bone marrow rescue; A, amplified; AWD, alive with disease; BM, bone marrow; b, bones; CAV, cyclophosphamide-doxorubicin-vincristine; carbo-carboplatin; CR, complete remission; CRA, cis-retinoic acid; CSF, cerebrospinal fluid; CSI, 2100 cGy radiation therapy; Dx, diagnosis; F, female; irino, irinotecan; LDH, serum lactic dehydrogenase (U/L); LM, leptomeningeal; LN, lymphadenopathy; M, male; mon, months; MYCN, N-myc amplification status; NB, not-amplified; NB, neuroblastoma; P/VP, cisplatin-etoposide; R, right; RT, S, surgical resection on bulky disease; t-AML, treatment-related acute myelogenous leukemia; thio, thiotepa-carboplatin; tmz, temozolomide; VP, etoposide

* not yet calcula

Table 3
Overall Summary of 21 Patients Treated with cRIT-based CNS Treatment Plan since 2003

Characteristics	N
Median Age at initial diagnosis (mon)	29.3
Median Time to detection of CNS disease (mon) from initial diagnosis	21.4
Prior treatment with myeloablative chemotherapies	13
Isolated CNS disease as first relapse	16
Isolated CNS disease as second relapse	3
CNS and systemic NB	2
LM	2
Single parenchymal lesion	11
Multiple parenchymal lesions	7
Both LM and parenchymal	2
CSF cytology positive	1
Gross total surgical resection	13
Treated with 21 Gy craniospinal irradiation	16
Number patients alive	17
Number in CR	16 (7-74 mon)
Death from isolated CNS NB	0
Death from systemic NB	2
Death from CNS and systemic NB	1
Median time to death from CNS detection (mon) (4 patients)	26.5