A Safety and Feasibility Trial of ^{131}I-MIBG in Newly Diagnosed High-Risk Neuroblastoma: A Children's Oncology Group (COG) Study

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Abbreviations

^{131}I-MIBG	^{131}I-metaiodobenzylguanidine
ASCR	autologous stem cell rescue
Bu/Mel	busulfan/melphalan
CEM	carboplatin, etoposide and melphalan
COG	Children's Oncology Group
CR	complete response
EBRT	external beam radiation therapy
EFS	event-free survival
MIBG	Meta-iodobenzylguanidine
MTD	maximum tolerated dose
PBSC	peripheral blood stem cells
PD	progressive disease
PR	partial response
SE	standard error

SOS	sinusoidal obstruction syndrome
VGPR	very good partial response

ABSTRACT

Introduction: ^{131}I-metaiodobenzylguanidine (^{131}I-MIBG) is effective in relapsed neuroblastoma. The Children's Oncology Group (COG) conducted a pilot study (NCT01175356) to assess tolerability and feasibility of induction chemotherapy followed by ^{131}I-MIBG therapy and myeloablative busulfan/melphalan (Bu/Mel) in patients with newly diagnosed high-risk neuroblastoma.

Methods: Patients with MIBG-avid high-risk neuroblastoma were eligible. After the first two patients to receive protocol therapy developed severe sinusoidal obstruction syndrome (SOS), the trial was re-designed to include an ^{131}I-MIBG dose escalation (12, 15, 18 mCi/kg), with a required 10-week gap before Bu/Mel administration. Patients who completed induction chemotherapy were evaluable for assessment of ^{131}I-MIBG feasibility; those who completed ^{131}I-MIBG therapy were evaluable for assessment of ^{131}I-MIBG+Bu/Mel feasibility.

Results: Fifty-nine of 68 patients (86.8%) who completed induction chemotherapy received ^{131}I-MIBG. Thirty-seven of 45 patients (82.2%) evaluable for ^{131}I-MIBG+Bu/Mel received this combination. Among those who received ^{131}I-MIBG after revision of the study design, one patient per dose level developed severe SOS. Rates of moderate to severe SOS at 12, 15

and 18 mCi/kg were 33.3%, 23.5%, and 25.0%, respectively. There was 1 toxic death. The ^{131}I-MIBG and ^{131}I-MIBG+Bu/Mel feasibility rates at the 15 mCi/kg dose level designated for further study were 96.7% [95% CI: (83.3%, 99.4%)] and 81.0% [95% CI: (60.0%, 92.3%)].

Conclusion:

This pilot trial demonstrated feasibility and tolerability of administering ^{131}I-MIBG followed by myeloablative therapy with Bu/Mel to newly diagnosed children with high-risk neuroblastoma in a cooperative group setting**,** laying the groundwork for a cooperative randomized trial (NCT03126916) testing the addition of ^{131}I-MIBG during induction therapy.

Introduction

Metastatic neuroblastoma continues to be a therapeutic challenge, despite improvements in event-free survival (EFS) with induction chemotherapy, surgery, myeloablative therapy with autologous stem cell rescue (ASCR), local radiation, differentiation therapy and immunotherapy[1,2]. Inadequate response is seen in ~20% of patients before myeloablative therapy, and predicts a lower EFS[1-7]. Novel therapies early in treatment are required to improve survival.

Meta-iodobenzylguanidine (MIBG), a norepinephrine analog taken up by 90% of neuroblastomas, is concentrated selectively in sympathetic nervous tissue. MIBG labeled

with iodine-131 (^{131}I-MIBG) has activity against relapsed and newly diagnosed neuroblastoma[8-11]. Early phase trials of ^{131}I-MIBG in relapsed/refractory neuroblastoma showed response rates up to 37%[7,12] with dose-limiting hematologic toxicity abrogated by ASCR[7]. A single institution study tested combining lower dose ^{131}I-MIBG with chemotherapy induction[13].

The feasibility of combining ^{131}I-MIBG with myeloablative carboplatin, etoposide and melphalan (CEM) after induction has been demonstrated in relapsed/refractory patients in phase 1 and 2 studies[14-19]. A few single institution studies of relapsed/refractory neuroblastoma also followed ^{131}I-MIBG with a Bu/Mel consolidation[20-22]. Based on a European randomized trial showing that BuMel consolidation after chemotherapy induction resulted in superior EFS compared to CEM[4], we selected Bu/Mel for our study. We hypothesized that the optimal time to treat with ^{131}I-MIBG would be in first response, and therefore designed the current trial, which is the first cooperative group trial inserting ^{131}I-MIBG as part of induction therapy. This Children's Oncology Group (COG) study for patients with newly diagnosed high-risk neuroblastoma was designed to assess the tolerability and feasibility of delivering ^{131}I-MIBG at end-induction followed by a consolidation regimen of myeloablative Bu/Mel and local external beam radiation therapy (EBRT) in a multi-institution setting.

Patients and Methods

Accrual to COG ANBL09P1 (NCT01175356) occurred from 2011-2015 at 23 institutions, including those with (n=13) and without (n=10) ^{131}I-MIBG therapy administration capability. This trial was approved by the Pediatric Central Institutional Review Board of the National Cancer Institute and local institutional review boards. Written informed consent (and assent as appropriate) was obtained. Data cut-off for analyses was September 30, 2019.

Eligible patients were 1-30 years old at the time of diagnosis and had high-risk neuroblastoma due to: tumor *MYCN* amplification with International Neuroblastoma Staging System stage 2-4; Stage 3 disease with centrally confirmed unfavorable histology[23] and >18 months of age at diagnosis; or Stage 4 disease diagnosed at age >18 months; or Stage 4 disease and age 12-18 months with tumors demonstrating centrally confirmed unfavorable biology (*MYCN* amplification, unfavorable histology and/or DNA index=1). Eligibility requirements included normal organ function, confirmation of MIBG-avid disease, and the ability to collect a minimum of 4 million CD34+ peripheral blood stem cells (PBSC) per kg body weight. In order to allow for enrollment from smaller centers that may not have ready access to MIBG scans, documentation of MIBG avidity was not required before enrollment but had to be confirmed before induction cycle 2. Patients with MIBG non-avid tumors were declared ineligible and removed from protocol therapy. For those who remained on study, subsequent MIBG scans were required prior to surgery, at the end of induction, just prior to myeloablative Bu/Mel, post consolidation and at the end of post consolidation treatment.

All patients received induction chemotherapy (Figure 1A). Patients on the original iteration of the protocol (Iteration 1) then received 18 mCi/kg ^{131}I-MIBG (Jubilant Draximage, Quebec, Canada) with vincristine and irinotecan followed by ASCR (≥2 x 10^6 CD 34+ cells/kg) two

weeks later[24]. Patients received myeloablative Bu/Mel ≥5 weeks later. Patients could proceed to ^{131}I-MIBG therapy and Bu/Mel regardless of Curie score documented prior to these interventions. Unacceptable sinusoidal obstruction syndrome (SOS; defined below in the statistical methods section) was observed in the first two patients who received vincristine, irinotecan, and ^{131}I-MIBG followed by Bu/Mel. Therefore, the protocol was amended and remaining previously enrolled patients were taken off protocol therapy.

Patients enrolled following a major protocol amendment (protocol Iteration 2) received induction chemotherapy followed by ^{131}I-MIBG alone, with ASCR 2 weeks later in cohorts of 12, 15 and 18 mCi/kg (444, 555, or 666 MBq/kg) (Figure 1B). While toxicity was being evaluated at the 15 and 18 mCi/kg dose levels, patients were assigned to the next lower ^{131}I-MIBG dose level that had already been shown to be safe. This permitted ongoing assessment of the feasibility of administering protocol therapy, however as a result, different numbers of patients were enrolled at each ^{131}I-MIBG dose level. Patients unable to receive ^{131}I-MIBG therapy due to a pause in dose assignments while safety assessments were being performed were removed from protocol therapy; those patients were not included in the assessment of feasibility. Patients who received an MIBG dose which varied by more than 10% of the assigned dose were removed from protocol therapy.

Subsequent myeloablative Bu/Mel with ASCR occurred at least 10 weeks from ^{131}I-MIBG administration. All patients who received ^{131}I-MIBG had an indwelling urinary catheter for bladder protection, potassium iodide as thyroid protection for six weeks, and underwent whole body dosimetry[18]. A complete disease evaluation was performed before and upon

completion of consolidation therapy per International Neuroblastoma Response Criteria[25]. Post-consolidation immunotherapy with anti-GD2 monoclonal antibody and isotretinoin was recommended for all patients[26].

Statistical Methods

Feasibility for administration of ^{131}I-MIBG and feasibility for administration of ^{131}I-MIBG followed by Bu/Mel were determined using patients from both iterations of the protocol. The feasibility rate for administration of ^{131}I-MIBG was defined as the number of patients with MIBG-avid disease assigned to an ^{131}I-MIBG dose level at induction Cycle 5 to whom ^{131}I-MIBG was administered divided by the total number of patients with MIBG-avid disease who could have been assigned to an ^{131}I-MIBG dose level. The denominator included patients who went off protocol therapy before receiving a dose assignment, but excluded those who could not continue due to periods of ^{131}I-MIBG therapy suspension for toxicity evaluation. The ^{131}I-MIBG with Bu/Mel feasibility rate was defined as the proportion of patients with MIBG-avid disease who received the assigned ^{131}I-MIBG, then Bu/Mel divided by the number of patients who received ^{131}I-MIBG and met criteria to receive myeloablative Bu/Mel. If patients developed progressive disease (PD) prior to Bu/Mel, they were not eligible for transplant and not included in the feasibility determination as patients with PD were not eligible to receive myeloablative Bu/Mel. The treatment was deemed feasible if the upper bound of a 95% confidence interval on the ^{131}I-MIBG feasibility rate and the ^{131}I-MIBG and Bu/Mel feasibility rate were each ≥80%. We also assessed the financial impact of traveling for ^{131}I-MIBG therapy by comparing the

total cost of travel, housing, food, and lost wages for patients who traveled to another institution to receive ^{131}I-MIBG to an estimated annual per capita income. Treatment was considered feasible if the total costs were <10% of total income, deemed as acceptable, although there is no established standard percentage.

Tolerability was determined only for patients enrolled in Iteration 2, both for administration of ^{131}I-MIBG and for administration of ^{131}I-MIBG followed by Bu/Mel. The study incorporated a dose-finding component to determine the maximum tolerated dose (MTD) of ^{131}I-MIBG in cohorts of up to 6 patients using a modified Rolling Six design, as described above and in Figure 1B. Tolerability of the regimen at each dose level could be further assessed in cohorts of up to 18 patients. Common Terminology Criteria for Adverse Events version 4.0 was used to assess toxicity. A composite definition of SOS[19] defined moderate SOS as: serum total bilirubin >2.0 mg/dL, **plus** ≥2 of the following findings from the beginning of ^{131}I-MIBG to within 28 days after transplantation: hepatomegaly with right upper quadrant pain, ascites, or weight gain >5% above baseline. Severe SOS was defined as above **plus** a specific organ failure: Grade 4 hepatic failure; or Grade 3 hypoxia for >48 hours, with ventilatory support not clearly attributable to another cause; or Grade 3 creatinine or Grade 4 renal dysfunction not clearly attributable to another cause. In addition, combined toxic death rate associated with ^{131}I-MIBG and Bu/Mel therapy, neutrophil engraftment rate after ^{131}I-MIBG and after Bu/Mel, and Grade 4 renal, pulmonary, and cardiac toxicity were monitored. If at any time ≥4 patients at any ^{131}I-MIBG dose level who were evaluable for the tolerability of ^{131}I-MIBG experienced a

severe toxicity as defined above, from start of ^{131}I-MIBG therapy through Day +28 post myeloablative Bu/Mel ASCR, then the treatment would be deemed not tolerable at that ^{131}I-MIBG dose level.

Exploratory aims included assessment of the relationship of SOS occurrence to busulfan exposure and to whole body ^{131}I-MIBG radiation dose[27]. In addition, Curie score[5,28] at diagnosis and end-induction, response rate[25] at end-induction and end-consolidation, and EFS were determined. For the analyses of EFS, time to event was calculated from the date of study enrollment to first occurrence of relapse, progression, second malignancy, or death; patients without event were censored on the date of last contact. EFS estimates were generated per Kaplan-Meier[29] with standard error (SE) per Peto[30] and reported as the estimate ± SE.

Results

Patient characteristics

A total of 99 patients were enrolled (Figure 2). Eleven patients were enrolled on Iteration 1 and eighty-eight patients on Iteration 2. One patient on Iteration 2 was deemed ineligible (incorrect diagnosis). The characteristics of the remaining patients are shown (Table 1). Sixty-eight patients were evaluable for feasibility of ^{131}I-MIBG therapy (three from Iteration 1 and 65 from Iteration 2) and 45 patients were evaluable for the feasibility of ^{131}I-MIBG plus Bu/Mel (two in Iteration 1; 43 in Iteration 2). Thirty-five patients were evaluable for tolerability of ^{131}I-MIBG plus myeloablative Bu/Mel (all from Iteration 2). The required number of stem cells were successfully harvested for all patients. Fourteen patients on Iteration 2

subsequently enrolled on COG ANBL0032 and received chimeric anti-GD2 monoclonal antibody post-consolidation.

Of the eleven patients enrolled on Iteration 1 (Figure 2), three received ^{131}I-MIBG; however, the first two patients developed severe SOS with myeloablative Bu/Mel and the trial was suspended. The third patient treated with ^{131}I-MIBG during Iteration 1 was therefore removed from protocol therapy, as were the eight patients who had been enrolled prior to trial suspension who had not yet received ^{131}I-MIBG . The protocol was amended as described above, and 87 eligible patients were enrolled during Iteration 2. Of these, 31 did not receive ^{131}I-MIBG. This included 22 patients not included in feasibility assessment (20 patients who were not assigned an ^{131}I-MIBG dose during periods of ^{131}I-MIBG therapy suspension for toxicity evaluation and two patients whose tumors were MIBG non-avid), in addition to nine patients who did not receive ^{131}I-MIBG therapy due to physician or parent preference (Figure 2) and were included in the feasibility assessment. Thus, 65 patients from Iteration 2 (56 patients who received ^{131}I-MIBG therapy plus the nine patients above who did not) were evaluable for feasibility of ^{131}I-MIBG therapy. Of the 56 who actually received ^{131}I-MIBG, 3 patients received a dose higher than the protocol-specified dose, and were therefore inevaluable for tolerability and did not proceed to Bu/Mel. Of the 53 evaluable patients who received ^{131}I-MIBG, 10 patients did not proceed to Bu/Mel due to PD and were therefore not evaluable for feasibility of ^{131}I-MIBG plus myeloablative Bu/Mel since patients with PD were ineligible for Bu/Mel. Eight patients from Iteration 2 evaluable for feasibility did not proceed to ^{131}I-MIBG plus myeloablative Bu/Mel due to physician preference (n=5) or patient preference (n=3) but were included in the feasibility calculation in addition to the 35 patients from Iteration 2 who received ^{131}I-MIBG plus myeloablative Bu/Mel, allowing for 45 patients evaluable for feasibity of ^{131}I-MIBG plus myeloablative Bu/Mel (2 from iteration 1 and 43 from iteration 2). In addition, 35 patients (all from Iteration 2) were evaluable for tolerability of ^{131}I-

MIBG plus myeloablative Bu/Mel. Median whole-body radiation doses for patients treated on Iteration 2 was 199 cGy (range 106-428) (Table 2). The median time from ASCR after ^{131}I-MIBG to Day 0 of ASCR after myeloablative Bu/Mel was 69 days (range 63-125).

Feasibility

Fifty-nine of 68 patients (86.8%) evaluable for the feasibility of ^{131}I-MIBG endpoint received ^{131}I-MIBG (three in Iteration 1; 56 in Iteration 2), while nine additional patients met criteria to receive ^{131}I-MIBG but were removed from protocol therapy due to physician/parent preference (Figure 2). These nine patients were divided between MIBG capable centers and non-MIBG capable centers. Thirty-seven of 45 patients (82.2%) evaluable for the ^{131}I-MIBG plus Bu/Mel feasibility analysis received this combination (two in Iteration 1; 35 in Iteration 2). The ^{131}I-MIBG and ^{131}I-MIBG plus Bu/Mel feasibility rates at 15 mCi/kg, the dose selected for further study, were 96.7% [95% Wilson confidence interval (CI): (83.3%, 99.4%)] and 81.0% [95% CI: (60.0%, 92.3%)], all meeting critera for feasibility (>80%).

The family/caregiver MIBG questionnaire was completed by 20 eligible families out of 29 (69.0%) who traveled to another institution to receive ^{131}I-MIBG therapy (Supplemental Table 1). Median number of days at the MIBG-treating institution was 7 (range 3-18). Median percentage of average total income encompassed by the total of travel + housing + food + lost wages was 6.4% (range 2.4%-16.4%) (Supplemental Table 2). No patient who was assigned an MIBG dose was unable to receive ^{131}I-MIBG due to insurance refusal, including the 25.5% (25/98) of patients with public insurance.

Tolerability

Of the 53 evaluable patients in Iteration 2 (when evaluated before administration of Bu/Mel), there were no patients with Grade ≥4 non-hematologic toxicity or SOS, and only three patients with Grade 3 toxicities, all of which completely resolved (Supplemental Table 3).

Thirty-five patients from Iteration 2 received Bu/Mel consolidation (Table 2). There were no toxic deaths at any dose. One patient developed Grade 4 hypoxia with pleural effusion due to SOS attributed to Bu/Mel conditioning. One patient developed pulmonary hypertension and cardiac arrest 2 months after Bu/Mel; this patient was successfully resuscitated and the treating physician did not attribute the event to Bu/Mel. Other toxicities following the combination of ^{131}I-MIBG and Bu/Mel in Iteration 2 were as expected: 14.3% developed Grade 3-4 febrile neutropenia while 34.3% developed mucositis (Supplemental Table 3). The regimen in Iteration 2 was deemed tolerable, as there were no toxic deaths, fewer than 4 patients at any dose level had Grade 4 non-hematological toxicity, and engraftment was rapid post-Bu/Mel, with all patients reaching ANC >500 before day 28 post transplant.

Eleven of the 35 patients (31.4%) receiving Bu/Mel in Iteration 2 developed SOS of any severity (Table 3). Overall rates of moderate to severe SOS at the 12, 15 and 18 mCi/kg doses were 33.3%, 23.5%, and 25.0% respectively. Patients with moderate to severe SOS received defibrotide for a median of 22 days (range 5-39). The Wilcoxon rank-sum test showed no differences in whole body radiation dose (p=0.7554), busulfan area under the curve (AUC) (p=0.1827), and median number of days (70 vs. 68) between administration of ^{131}I-MIBG and Bu/Mel among patients that did vs. did not develop SOS (p=0.4970). By Fisher's exact test, there was no relationship between ^{131}I-MIBG dose per kg administered

(p=0.8899) or frequency of busulfan dose changes in those who developed SOS compared with those that did not (p=0.3928).

Response and EFS

Thirty-eight of 53 Iteration 2 patients (71.7%) evaluated for response after induction chemotherapy plus ^{131}I-MIBG therapy achieved an objective response (CR/VGPR/PR) (Table 4). Thirty-one of 34 (91.2%) were in CR/VGPR/PR at the end-consolidation. All of the patients who had a CR at end-induction also had a CR at end-consolidation; in addition, three patients who had a PR at end-induction had a CR at end-consolidation. Of the 38 patients who had an objective response at end-induction, only two developed PD at end-consolidation (Table 4; Supplemental Table 4). The median Curie score at the end of induction with MIBG was 1 (0, 24) (Table 2); a total of 29/53 (61.7%) patients had a Curie score of <3 at the end of induction plus MIBG (Table 2). Only one of the 10 patients who had PD before myeloablative BuMel had complete resolution of MIBG avidity after ^{131}I-MIBG therapy (Supplemental Table 5). One-year EFS for all eligible patients was 74.2±4.4% (n=98) (Supplemental Figure 1). The 1-year EFS for those who received ^{131}I-MIBG therapy on Iteration 2 was 71.4±6.0% (n=56). The 1-year and 3-year EFS for those on Iteration 2 who received ^{131}I-MIBG and Bu/Mel were 91.4±4.7% (n=35) and 60.0±8.3%, respectively (Supplemental Figure 1).

Discussion

The addition of ^{131}I-MIBG therapy during induction for patients with MIBG-avid high-risk neuroblastoma may decrease disease burden prior to myeloablative therapy and ultimately

improve EFS[31,32]. Our trial enrolled 99 high risk neuroblastoma patients from 23 institutions and myeloablative therapy after MIBG was administered to 37 high-risk patients treated from diagnosis, thereby demonstrating the feasibility and tolerability of administering ^{131}I-MIBG therapy during induction followed by myeloablative therapy with Bu/Mel in a cooperative group setting.

Feasibility benchmarks were met for administration of ^{131}I-MIBG therapy, with 86.8% of patients assigned an MIBG dose able to receive this therapy, and 82.2% of eligible patients able to receive ^{131}I-MIBG therapy and planned myeloablative Bu/Mel consolidation therapy. Even including the 18 patients on Iteration 2 who received MIBG but either developed PD or chose not to proceed to Bu/Mel, the feasibility rate would be 37/63 (58.7%), comparable to SIOPEN and COG trials where only about 50% of patients entered were randomized prior to myeloablative therapy at the end of induction[1,4]. This study showed that it was feasible to transfer patients to another institution for ^{131}I-MIBG therapy within the desired timeframe and transfer them back to their primary institution for stem cell support, with subsequent administration of myeloablative Bu/Mel conditioning and ASCR. There are now >20 institutions capable of administering high-dose ^{131}I-MIBG to children in North America, further improving access to this therapy for newly diagnosed patients.

Concern about the burden of cancer treatment on families is mounting[33-35]. Despite required travel for MIBG therapy for a portion of patients on this trial, the estimated economic burden to families was below the *a priori* study threshold of 10% of median annual salary, and extended time away from home was not required. While charitable support for families was not taken into account during assessment of economic impact, no patients in this trial were

denied treatment due to lack of insurance coverage.

This regimen was also shown to be tolerable in the frontline setting. The cohort now described comprises the largest group of patients with high-risk neuroblastoma treated from diagnosis to undergo ^{131}I-MIBG followed by Bu/Mel. While stopping rules outlined in the protocol were not met, concern regarding the development of severe SOS in the first two patients on this study led to a major amendment to remove the concomitant use of vincristine and irinotecan with ^{131}I-MIBG, and to extend the time between ^{131}I-MIBG and Bu/Mel. Following this change, 11 cases of SOS occurred, however only three cases were severe. In previous studies in patients with relapsed neuroblastoma in whom ^{131}I-MIBG was delivered two weeks prior to a myeloablative CEM conditioning regimen and ASCR, a 12% incidence of SOS was observed[19,36]. In two small studies of patients with relapsed/refractory neuroblastoma who received ^{131}I-MIBG followed by myeloablative Bu/Mel ASCR, there were 2/17 with severe SOS[21,22]. In an international SIOPEN trial of Bu/Mel vs CEM for high-risk neuroblastoma, 60 of 267 (22%) patients who received Bu/Mel developed SOS with Bearman toxicity Grades 1–3 compared with 21 of 239 (9%) receiving CEM[4]. In a single institution retrospective study of CEM vs Bu/Mel in high-risk neuroblastoma, SOS was observed in 7/44 CEM (15.9%) and 5/21 Bu/Mel (24%) patients[37]. The overall SOS rate of 31.4% in our study and the 8.6% rate of severe SOS were both apparently higher than in the SIOPEN study of Bu/Mel alone (4%), suggesting that the proximity of MIBG to Bu/Mel may increase the risk of SOS. No correlation between development of SOS and busulfan AUC, whole body radiation dose or MIBG dose administered was found in our study. While our data show that administration of ^{131}I-MIBG followed by Bu/Mel is tolerable, close monitoring for SOS is required.

The response rate at the end of induction in our study was similar to rates associated with regimens not including ^{131}I-MIBG[1,3]. Importantly, 18.9% of patients developed progressive disease during the interval between MIBG and Bu/Mel, which suggests this may not be the optimal timing of ^{131}I-MIBG therapy due to the required delay in starting consolidation therapy. Because administration of ^{131}I-MIBG therapy early in induction may improve extent of tumor resection[32] and end-induction response, earlier administration of this component of therapy may be advantageous. Finally, results of a randomized COG trial indicate that tandem CEM-based transplant improves EFS compared to single CEM transplant[1]. The potential for SOS with ^{131}I-MIBG in close proximity to Bu/Mel led to selection of ^{131}I-MIBG administered earlier during induction in an ongoing randomized Phase 3 COG trial that includes tandem transplant (NCT03126916). In the Phase 3 COG trial, the dose of 15 mCi/kg was selected to be conservative given the risk of SOS, since there was no appreciable difference in response and toxicity from the 18 mCi/kg dose.

Conclusion:

This pilot trial demonstrated the feasibility and tolerability of administering ^{131}I-MIBG followed by myeloablative therapy with Bu/Mel to newly diagnosed children with high-risk neuroblastoma in a cooperative group setting, thus laying the groundwork for a large randomized trial evaluating the impact of adding ^{131}I-MIBG during induction therapy.

Conflict of Interest: The authors have no known competing financial interests/personal relationships to declare.

All authors contributed to this paper substantively.

Children's Oncology Group Data Sharing Policy

The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to:

datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use.

For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

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Figure Legends

Figure 1. Treatment plan

Figure 1A. Treatment Schema

Patients received 2 cycles of topotecan (1.2 mg/m^2/dose x 5 days) and cyclophosphamide (400 mg/m^2/dose x 5 days) (each cycle lasting 21 days assuming blood count recovery), followed by PBSC harvest; cycle 3 of cisplatin (50 mg/m^2/dose x 4 days) and etoposide (200 mg/m^2/dose x 3 days); cycle 4 of cyclophosphamide (2100 mg/m^2/dose x 2 days), doxorubicin (25 mg/m^2/dose x 3 days) and vincristine (the lower dose of 0.67 mg/m^2/dose OR 0.022 mg/kg/dose x 3 days) followed by tumor imaging and MIBG scan and attempted surgical resection; and cycle 5 cisplatin and etoposide. Patients on the first iteration of the protocol (Iteration 1) then received ^{131}I-MIBG at 18 mCi/kg along with vincristine (2 mg/m^2/dose x 1 day; max 2 mg) and irinotecan (50 mg/m^2/dose x 5 days; max 100 mg) followed 2 weeks later by ASCR, then 5 weeks later by myeloablative Bu/Mel consolidation plus ASCR. Patients enrolled on Iteration 2 received ^{131}I-MIBG (3-6 weeks from the start of cycle 5) at either 12 mCi/kg, 15 mCi/kg, or 18 mCi/kg (without vincristine or irinotecan) using a modified rolling six design, followed by ASCR 2 weeks later. A mandatory break of 10-12 weeks from ^{131}I-MIBG infusion was required prior to myeloablative Bu/Mel consolidation plus ASCR. Patients received intravenous busulfan every six hours for 16 doses from Day -6 to Day -3 (with mandatory pharmacokinetic (PK) guided dosing), and melphalan (140 mg/m2) on Day -1. After recovery from acute toxicities, patients received external beam radiation therapy (21.6 Gy) to the primary site and up to five MIBG-avid sites[1], followed by post-consolidation therapy of the investigator's choice, though anti-GD2 antibody therapy was recommended.

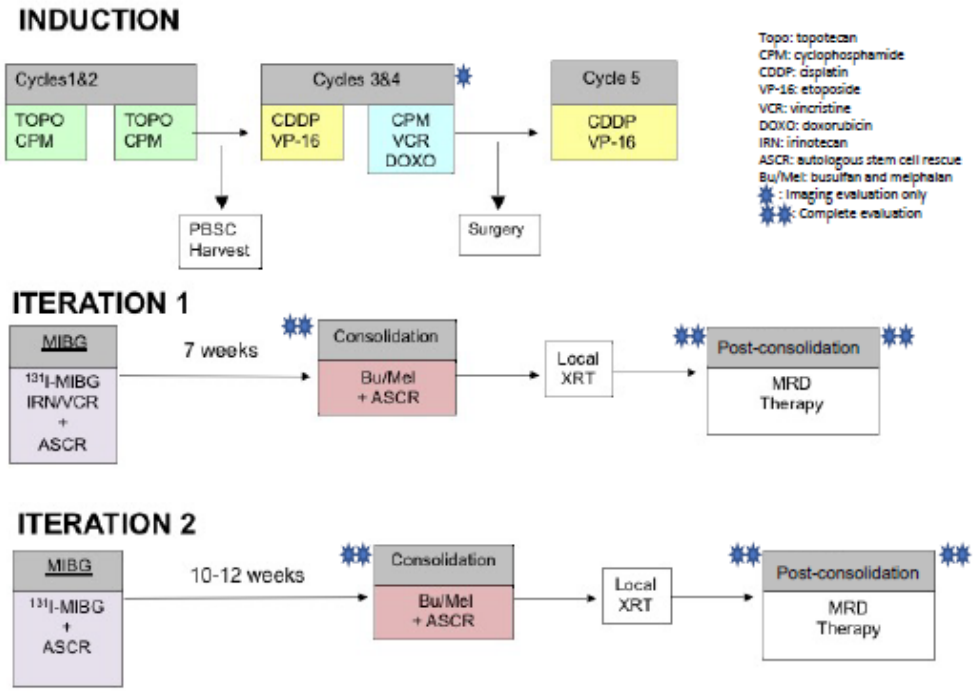

Figure 1B. Dose escalation plan

The initial cohort of patients in Iteration 2 received 15 mCi/kg ^{131}I-MIBG followed by Bu/Mel. While determining safety at this dose, subsequent patients received ^{131}I-MIBG at a dose of 12 mCi/kg upon completion of induction chemotherapy. Once 15 mCi/kg ^{131}I-MIBG was determined to be safe, a dose of 18 mCi/kg ^{131}I-MIBG was similarly assessed. While toxicities associated with 18 mCi/kg ^{131}I-MIBG followed by Bu/Mel were being evaluated, subsequent patients received a dose of 15 mCi/kg. A maximum of 18 patients were to be treated with ^{131}I-MIBG plus Bu/Mel on any dose level. While therapy tolerability was being assessed, up to 18 patients could receive 12 mCi/kg of ^{131}I-MIBG, or the highest proven tolerable dose.

Figure 2. Consort diagram for ANBL09P1

Feasibility evaluations included eligible patients from Iteration 1 (n=11) and Iteration 2 (n=87). Tolerability evaluations only included patients from Iteration 2. Of eligible patients, 68 were evaluable for feasibility of ^{131}I-MIBG (3 from Iteration 1 and 65 from Iteration 2) and 45 for feasibility of ^{131}I-MIBG + Bu/Mel (2 from iteration 1 and 43 from Iteration 2). Patients from Iteration 2 evaluable for tolerability were: ^{131}I-MIBG (n=53); ^{131}I-MIBG + Bu/Mel (n=35).

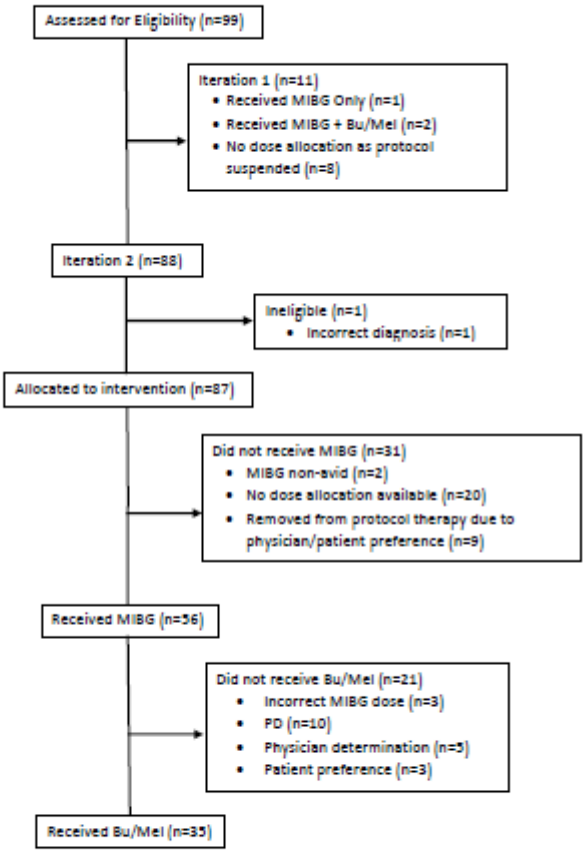

Table 1: Patient Characteristics

	n (%)[#]		
	Eligible (n=98)	**Iteration 1 (n=11)**	**Iteration 2 (n=87)**
Sex (M:F)	59:39	5:6	54:33
Median age in months (range)	43.3 (14.7-143.6)	37.8 (16.8-135.1)	47.8 (14.7-143.6)
INSS 2/3	6 (6.1%)	1 (9.1%)	5 (5.7%)
INSS 4	92 (93.9%)	10 (90.9%)	82 (94.3%)
MYCN			
Amplified	24 (27.9%)	3 (27.3%)	21 (28.0%)
Non-Amplified	62 (72.1%)	8 (72.7%)	54 (72.0%)
Unknown	12	0	12
Grade			
Differentiated	1 (1.2%)	1 (11.1%)	0 (0.0%)
Undifferentiated/poorly differentiated	84 (98.8%)	8 (88.9%)	76 (100.0%)
Unknown	13	2	11

INPC Favorable Unfavorable Unknown	3 (3.5%) 82 (96.5%) 13	2 (22.2%) 7 (77.8%) 2	1 (1.3%) 75 (98.7%) 11
Median Curie Score at Diagnosis (range)	20 (0-28)*	17 (1-28)	20 (0-28) †

Percentages calculated based on patients with data available for the given characteristic.

*Two patients found to be non-avid for MIBG, N=96.

† N=85.

Table 2: Evaluable Patients in Iteration 2 Treated with MIBG with or without Bu/Mel

^{131}I-MIBG Dose Level	**Received ^{131}I-MIBG (n)**	**Whole Body Radiation Dose[a] (cGy) Median (range)**	**Curie Score at Diagnosis[b] Median (range)**	**Curie Score Post-MIBG[c] Induction Median (range)**	**Patients with Curie Score <3 Post-MIBG[c] Induction (n, %)**	**MIBG + Bu/Mel (n)**
12 mCi/kg	7	183 (113, 213)	23 (1, 28)	0 (0,3)	4 (80.0%)	6
15	26[d]	216 (109,	19 (1, 28)	1 (0, 24)	14 (58.3%)	17

mCi/kg		428)				
18 mCi/kg	20	197.5 (106, 362)	22 (4, 28)	2 (0, 11)	11 (61.1%)	12
Total	53	199 (106, 428)	20 (1, 28)	1 (0, 24)	29 (61.7%)	35

[a] Seven, 24, 18 patients evaluated respectively for the whole body radiation dose in 12, 15, and 18 mCi/kg cohort

[b] Seven, 25, 20 patients evaluated respectively for the Curie score at diagnosis in 12, 15, and 18 mCi/kg cohort

[c] Five, 24, 18 patients evaluated respectively for the Curie score post-MIBG in 12, 15, and 18 mCi/kg cohort

[d] Excludes 3 patients that received ^{131}I-MIBG >110% of dose assigned

Table 3: Patients with SOS in Iteration 2

SOS Case	**SOS Severity**	**^{131}I-MIBG Dose (mCi/kg)**	**Whole Body Radiation (cGy)**	**Busulfan AUC (μM/L/min)[a]**	**Busulfan Dose Adjusted[b]**	**MIBG to Bu/Mel (days)[c]**
1	Severe	12	213	960	NC	65
2	Moderate	12	113	1002	D	68
3	Severe	15	253	1137	NC	69
4	Moderate	15	159	859	I	70

5	Moderate	15	160	1153	D	70
6	Moderate	15	262	1085	NC	69
7	Mild	15	256	756	I	70
8	Mild	15	347	910	NC	70
9	Severe	18	161	1134	NC	64
10	Moderate	18	199	1021	NC	69
11	Moderate	18	188	807	I	66

[a] All blood levels were after the first dose except cases 8 and 11, which were performed after a first and third dose and a test dose, respectively. Pharmacokinetics were performed as per institutional guidelines, to achieve an area under the curve (AUC) for busulfan of 900 to 1500 micromole/liter/minute.

[b] Abbreviations: increase = I. decrease = D. no change = NC. Not available = N/A

[c] Calculated as days from ASCR post ^{131}I-MIBG to days ASCR post myeloablative Bu/Mel

Table 4: Response to ^{131}I-MIBG therapy and response to Bu/Mel consolidation during Iteration 2.

Response Post-BuMel		**Response Post-MIBG**							**Total**
		CR	**VGPR**	**PR**	**NR**	**MR**	**PD**	**NE**	
	CR	13	0	3	0	0	0	0	16
	VGPR	0	6	1	0	0	0	0	7

	PR	0	0	7	0	1	0	0	8
	NR	0	0	0	0	0	0	0	0
	MR	0	0	0	0	0	0	0	0
	PD	0	0	2	0	1	0	0	3
	NE	0	1	5	2	1	10	3	22*
Total		13	7	18	2	3	10	3	56[#]

*Of the 22 patients not evaluated, 1 patient was not evaluated post-BuMel, while the other 21 patients did not receive BuMel.

[#]3 patients of the 56 were not evaluated, leaving 53 evaluated patients

Abbreviations: CR, Complete Response; VGPR, very good partial response; PR, partial response; NR, No response, MR, mixed response, PD, progressive disease, evaluated according to International Neuroblastoma Response Criteria [25]. NE, no evaluation.