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Experiences from Introducing Standardized High Dose ^{131}I-mIBG Treatment of Children with Refractory Neuroblastoma: Differences in Effective Dose to Patients and Exposure to Caregivers

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Abstract

Aims: High dose ^{131}I-meta iodobenzylguanidine (^{131}I-mIBG) combined with radiosensitizing topotecan and peripheral blood stem cell support is a promising treatment regimen for children with neuroblastoma (NB). Here we present our first experiences, with particular focus on *in vivo* whole-body dosimetry and radiation exposure to family caregivers and hospital staff.

Methods: Five children with relapsed or refractory NB were treated during 2012-2014. ^{131}I-mIBG was administered in two fractions at two weeks apart, aiming for a total whole-body radiation-absorbed dose of 4 Gy. The ^{131}I-mIBG activity for the 2nd administration was calculated on the basis of the measured whole-body dose following the 1st administration. Patients were isolated in a lead-shielded room, and all caregivers and staff received radiation safety training, and carried an electronic personal dosimeter.

Results: The total administered activity ranged from 5.1 to 28.6 GBq (median: 22.9 GBq), resulting in effective whole-body doses ranging from 2.1 to 4.3 Gy (median: 3.8 Gy). Two out of five patients deviated from the anticipated dose exposure defined by the treatment protocol; one patient received 4.3 Gy after a single administration, and for one patient the total whole-body dose was lower than anticipated (2.1 Gy). Radiation dose to family caregivers ranged from 0.1 to 8.0 mSv. For staff members, the overall radiation dose was low, and provided no concern regarding personal dosimetry.

Conclusion: High-dose ^{131}I-mIBG treatment of children with NB has been successfully established at our institution. Radiation doses to caregivers and hospital staff are acceptable and in compliance with national and international guidelines. Two out of five patients deviated from the anticipated dose exposure, hence, accurate dosimetry-guidance during administration of high dose ^{131}I-mIBG treatment is necessary.

Keywords: Neuroblastoma; Radionuclide therapy; Nuclear medicine; Nuclear medicine therapy; Radiation safety; Dosimetry

Introduction

Neuroblastoma (NB) is a heterogeneous group of paediatric peripheral nerve tumours with heterogeneous biology and prognosis. High-risk tumours account for one half of NBs and are among the most difficult childhood malignancies to cure. Despite treatment protocols consisting of intensive multi-modality therapy, many children relapse, and the 5-year overall post relapse survival remains as low as 20% [1]. Hence, the need for improved treatment strategies is imperative. Several novel approaches are under investigation, such as immunotherapy [2] and implementation of new drugs for therapeutic targeting of MYCN/ALK [3]. Moreover, augmented 131I-meta iodobenzylguanidine (^{131}I-mIBG) therapy seems promising [4] by combining dosimetry and sensitizing chemotherapy during ^{131}I-mIBG treatment [5-7]. Many practical issues related to high radioactivity doses of ^{131}I-mIBG are challenging, and therefore institutions may be reluctant to establish this potentially lifesaving treatment modality for children with refractory or relapsed high risk NB.

A promising novel treatment regimen combines high dose ^{131}I-mIBG with radiosensitizing topotecan, followed by peripheral blood stem cell support [6]. The use of *in vivo* dosimetry facilitates precise whole-body radiation-absorbed dose measurement to increase treatment efficacy and reduce toxicity, and is in accordance with the "mIBG and Topotecan in Neuroblastoma" (MATIN) treatment protocol introduced by Gaze and colleagues [6]. Whole-body dosimetry is assumed as a surrogate for red marrow dosimetry, and hence, correlates with haematologic toxicity which is the primary side-effect of ^{131}I-mIBG therapy. In the MATIN protocol, up to two courses of ^{131}I-mIBG treatment are given in order to obtain a whole body radiation-absorbed dose of 4 Gy, i.e. the 50 % lethal dose (LD_{50}) for red marrow.

In addition to beta radiation for therapeutic purposes, ^{131}I emits high-energy gamma rays, and therefore, the patient must be kept in hospital isolation during the first phase of ^{131}I-mIBG therapy. Limited radiation exposure data for caregivers in this setting are available. Dose constraints to family members and close friends involved in ^{131}I-treatment is proposed by the European Commission to be 3 mSv for adults <60 years, and 15 mSv for adults >60 years per ^{131}I-treatment [8]. However, these levels are not expected to be applied to family and

close friends comforting children with neuroblastoma ^{131}I-mIBG treatment. Nursing staff involved with these patients are not classified as occupationally exposed personnel, and are therefore not monitored by the national personal dosimetry service. Hence, the dose constraint for this group is 1 mSv [9].

We present our first experiences establishing high-dose ^{131}I-mIBG therapy for children with high-risk NB at Oslo University Hospital (OUS). This rapport pays particular attention to the applied *in vivo* whole-body dosimetry and radiation exposure to family caregivers and hospital staff involved in ^{131}I-mIBG therapy.

Materials and Methods

All patients and caregivers gave written consent to participate in the treatment and publication (April 2015). Publication of our results was approved by the Research Surveillance unit at OUS.

Patients

Five children with relapsed or refractory NB in stable disease state were treated with ^{131}I-mIBG during 2012-2014 at our institution. Four of the children had received primary treatment according to the SIOPEN HR-NBL-1 protocol [10].

Patient	Disease stage	Sex and age at 131I-mIBG treatment [years]	Weight at 131I-mIBG treatment [kg]	Biology of NB	Distribution of 123I-mIBG positive lesions pre-treatment	Outcome status at time of consent for publication [months after 131I-mIBG treatment]
1	Refractory	Boy, 2	17	MYCN-not amplified, no chromosomal segmental aberrations	Diffuse skull uptake	Alive with positive mIBG uptake, off treatment, well [36 months]
2	Refractory	Girl, 2	13	MYCN-not amplified, no chromosomal segmental aberrations	Diffuse widespread skeletal uptake	Alive with positive mIBG uptake, off treatment, well [25 months]
3	Relapse x 1	Boy, 11	29	MYCN-not amplified, 11q23 deletion	Localized lesion left tibia	New localized relapse at another skeletal location 16 months later, under treatment [24 months]
4	Relapse x 3	Girl, 7	33	MYCN-gain, no other chromosomal segmental aberrations	Localized lesion L1	Alive with positive mIBG uptake, off treatment, well [22 months]
5	Relapse x 1	Boy, 8	35	MYCN-not amplified, 11q23 deletion, 17q gain	Minimal retro-peritoneal uptake and sparse uptake localized right tibia	Alive without signs of disease, still on treatment [5 months]

Table 1: Patient characteristics. Abbreviations: mIBG, meta iodobenzylguanidine.

Additional treatment of refractory and relapsed disease varied among the children. All patients had positive diagnostic ^{123}I-mIBG scintigraphy prior to treatment, as presented together with supplementary patient characteristics in Table 1.

Treatment protocol

^{131}I-mIBG treatment was conducted according to the MATIN protocol [6]. Two fractions of ^{131}I-mIBG were administered two weeks apart, aiming for a total whole-body radiation-absorbed dose of 4 Gy. The radiosensitizing chemotherapeutic agent, topotecan (0.7 mg/m^2), was given intravenously for five consecutive days during both fractions, starting simultaneously with ^{131}I-mIBG. In addition, to ensure haematological support, stem cells were harvested prior to treatment, and scheduled for reinfusion ~4 weeks after start of first fraction. Potassium-iodine was given for thyroid protection against free ^{131}-iodine. Whole-body planar and SPECT imaging was conducted 1-2 times post-administration to confirm tumour uptake.

The patients received anti-emetics, and were well hydrated and encouraged to void the bladder before start of ^{131}I-mIBG infusion. Each infusion was administered by two experienced nuclear medicine technologists over a period of ~90 minutes, with a medical doctor present to supervise the procedure in case of any side effects. The patients were instructed to remain in bed throughout the infusion. If needed the youngest children were given sedatives. Blood pressure, pulse and oxygen saturation were monitored. The dose administered during the 1st fraction was calculated according to patient body weight (444 MBq/kg), while the dose required for the 2nd fraction was calculated on basis of the whole-body radiation-absorbed dose following the 1st administration.

Whole-body dosimetry

To estimate the whole-body absorbed dose, an external gamma probe (SmartION Digital Survey Meter, Thermo Fisher Scientific, Waltham, USA) was placed at a fixed position approximately 2.5-3 meters from the patient bed. Dose rate recordings (μSv/hr) were conducted, starting with every hour for the first 8 hrs after induction, then every second hour for the next 24 hrs, every 3 hrs and so on until the patient was released from hospital (3-6 days). To account for the response time of the gamma probe, a 10-second reading was conducted at each time point. A background dose rate measurement was taken prior to each infusion. The dose rate recordings were conducted by the caregivers, after thoroughly training by a medical physicist. Care was taken to ensure that patient positioning was the same for each measurement, and if needed, the patient was instructed to void his/her bladder before each recording. For infants, caregivers were instructed to change the diapers. Also, instruction was given to ensure that there were no obstacles between the external probe and the patient. The measured dose rates were normalized to the initial injected activity, and plotted against time after injection. A bi-

exponential curve was fitted to the measured points in Matlab (MATLAB and Statistics Toolbox Release 2012b, The MathWorks, Inc., Natick, Massachusetts, United States), and accumulated activity was calculated by integrating the curve to infinity (Figure 1). The whole-body absorbed dose (Gy) was then calculated by multiplying the accumulated activity with the S-factor for children [11] as stipulated below.

$$S_{(w_b \leftarrow w_b)} = 1.34 \times 10^{-4} \times m_p{}^{-0.921}\ Gy\ MBq^{-1}h^{-1}$$

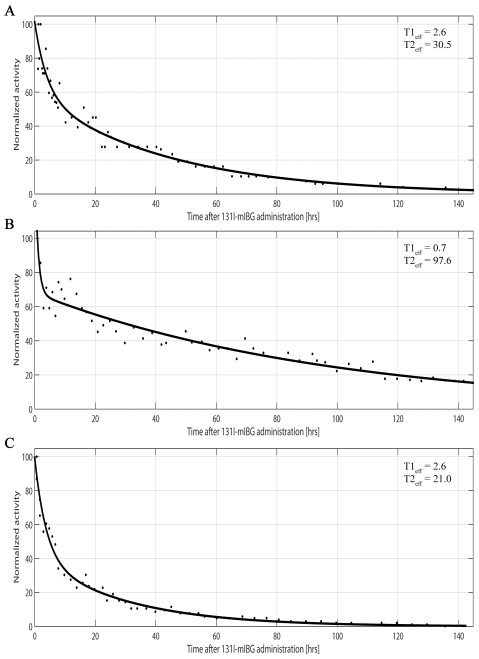

Figure 1: Pharmacokinetics of ^{131}I-mIBG for Patient 1 (A), Patient 2 (B) and Patient 5 (C). Data are shown for the first administration of ^{131}I-mIBG, and are normalized to the injected activity. Dotted points: dose rate measurements; solid line: bi-exponential fitting of data points. Abbreviations: T1eff, effective half-life for the first phase; T2eff, effective half-life for the second phase.

Where m_p is bodyweight (in kg). In addition, the effective half-lives (i.e. the combination of radioactive decay and biological excretion; Teff) were calculated for the initial phase (T1eff) and the later stage (T2eff) of the treatment.

Radiation protection and exposure

131-iodine emits both beta and gamma rays, and has a physical half-life of 8 days. During hospitalization, the patients were isolated in a customized room shielded with lead. All caregivers and paediatric staff received radiation safety training, and carried an electronic personal dosimeter (EPD; Thermo Fisher Scientific, Waltham, USA) when entering the patient room. The access to the treatment unit was limited to the assigned caregivers and staff. No children or pregnant women were allowed in the patient room. When possible, the caregivers and staff members were instructed to shield themselves either using a fixed lead-shielded wall next the patient's bed, or a mobile lead screen available in the patient room. Also, all involved partners were encouraged to keep distance to the patient, and limit the time spent with the patient to a minimum. For entertainment, the patients were allowed to bring some toys and books, and in particular, access to internet, television and videogames was crucial.

Approximately fifty percent of ^{131}I-mIBG is excreted through urine during the first 24 hrs [12], and therefore, the caregivers were instructed not to use the same ensuite bathroom as the patient. For infants, caregivers were instructed to always use disposable gloves when changing diapers, and to store used diapers in a lead-shielded freezer located in a nearby room. This room (with limited access) was also used for storage of bed linen, syringes, underwear etc., which had been in contact with the patient's body fluid. The level of residual radioactivity on these materials was checked by medical physicists to ensure compliance with local hospital radiation protection guidelines for waste management of radioactive materials (accepted level: dose rate <5 μSv/hr at 30 cm).

According to local hospital legislation, patients undergoing radionuclide therapy can be discharged from hospital when the dose rate at 1 meter is <30 μSv/hr.

Results

^{131}I-mIBG treatment

All patients tolerated the 131I-mIBG induction phase well, and no severe side effects were observed during the treatment. The total administered activity ranged from 5.1 to 28.6 GBq (median: 22.9 GBq; Figure 2). Only required staff were present in the isolation unit during the induction phase.

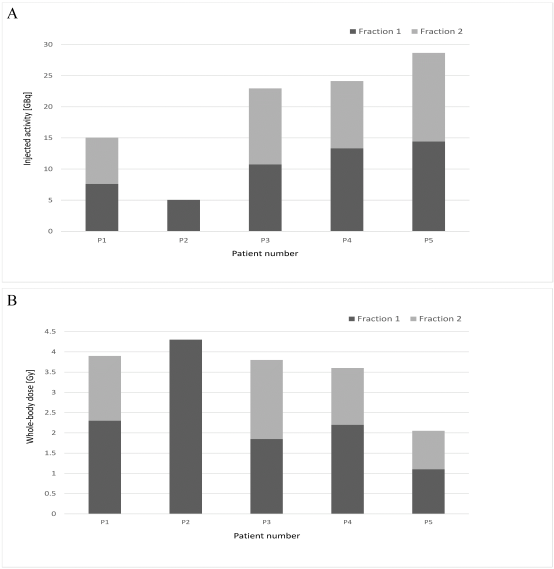

Figure 2: Administered ^{131}I-mIBG activity (A) and whole-body dosimetry data (B) following first (lower part of each bar) and second (upper part of each bar) administrations of ^{131}I-mIBG.

Whole body dosimetry

All caregivers reported that the dose rate recordings were straightforward and simple to perform. The maximum count rate measured was 110 μSv/hr, which is significantly below the upper measurement limit of the gammaprobe (500 mSv/hr). The number of measurements was sufficient to perform excellent bi-exponential fitting of data points (all fittings R2 >.92; Figure 1). The estimated effective whole-body doses varied significantly (range: 2.1-4.3 Gy; median: 3.8 Gy; Figure 2). For patient 2, the treatment was terminated after the first fraction due to high 131I-mIBG accumulation, which resulted in a high single-fraction radiation dose of 4.3 Gy. In contrast, the total effective dose for patient 5 after two fractions was lower than anticipated due to faster ^{131}I-mIBG wash out.

The pharmacokinetics of ^{131}I-mIBG for three of the patients are shown in Figure 1. As anticipated, Teff of ^{131}I-mIBG was much shorter for the initial phase than at the later stage of the treatment. For all patients who received two fractions, both T1eff and T2eff were shorter in the second round of treatment compared to the first (data not shown).

For patient 2, who received only one 131mIBG-fraction, T2eff was slower than in the other patients; reflecting a higher rate of ^{131}I-mIBG tissue accumulation. In contrast, patient 5 had faster wash out of ^{131}I-mIBG (i.e. shorter Teff) in both stages, which reflects the relatively low total whole-body dose reported for this patient.

The time of patient discharge varied from three to six days after administration, once the dose rate at 1 meter was <30 μSv/hr.

Radiation protection and exposure

The radiation dose to caregivers and staff was closely monitored by medical physicists during patient hospitalization, and the total received dose was in compliance with international and national guidelines for caregivers involved in radionuclide therapy [8]. Radiation dose to caregivers ranged from 0.1 to 8.0 mSv (Table 2). For patients 1 and 2, both <3 years, the caregivers received a statistical significantly higher radiation dose than for the older patients (two-sample t-test; $t(9.4)=7.69$; $p<0.001$). Hence, even though the older children received a much higher total dose, the closer and longer contact with infants led to a strong negative correlation between total administered radioactivity and mean radiation exposure to caregivers (Pearson's $r=-0.872$; $N=5$; $p<0.05$).

Patient	Age [years]	Total administered activity [GBq]	Number of caregivers	Radiation dose to caregivers [mSv]		Radiation dose to staff [mSv]	
				mean ± SD	Range (min-max)	mean ± SD	Max
1	2	15.1	3	5.7 ± 2.0	4.3 - 8.0	0.11 ± 0.08	0.26
2	2	5.1	6	5.5 ± 1.8	3.0 - 7.6	0.05 ± 0.06	0.18
3	11	22.9	6	0.6 ± 0.3	0.1 - 0.9	0.07 ± 0.12	0.47
4	7	24.1	3	1.7 ± 0.5	1.3 - 2.2	0.04 ± 0.07	0.3
5	8	28.6	3	0.8 ± 0.1	0.7 - 0.8	0.02 ± 0.04	0.18

Table 2: Radiation dose to caregivers and paediatric staff involved in ^{131}I-mIBG therapy.

The overall radiation dose to staff members (i.e. nurses and medical doctors) was low (Table 2), and provided no concern regarding personal dosimetry. The annual limit for hospital staff not included in the national personal dosimetry monitoring program is 1 mSv, and considering the low frequency of ^{131}I-mIBG treatments at our hospital together with interchange of involved staff, the measured dose values are considered as safe. The radiation exposure to the nuclear medicine technologists was negligible.

During hospitalization, all diapers were collected in plastic bags and stored in a lead-shielded freezer for a minimum of four weeks. No radioactive contamination (>5 μSv/hr) was reported on any of the patient's or caregivers' belongings at the time of patient discharge.

Discussion

High-dose ^{131}I-mIBG treatment of children with NB requires extensive considerations concerning radiation safety both for patients, their caregivers, and hospital staff. A multi-disciplinary team including medical doctors, nurses, nuclear medicine technologists and medical physicists is essential for paediatric radionuclide therapies.

^{131}I-mIBG treatment and dosimetry

The ^{131}I-mIBG treatment was conducted according to the MATIN protocol; two fractions of ^{131}I-mIBG injected two weeks apart in order to obtain an accurate whole-body radiation-absorbed dose of 4 Gy. For three out of five patients, the expected target radiation dose of about 4 Gy was achieved after two fractions (Figure 2). However, unexpectedly, the remaining two patients deviated significantly from the anticipated dose regimen. These relatively large differences in absorbed dose can be explained by variations in the pharmacokinetics of ^{131}I-mIBG, as observed by the dose-rate measurements. The kinetics of ^{131}I-mIBG is influenced both by normal physiological uptake and by the burden of noradrenalin transporter expressing tumour cells. For Patient 2, slower kinetic (i.e. high T2eff; Figure 1) correlated with a high tumour accumulation of ^{131}I-mIBG, and hence increased whole-body dose compared to the other patients. This patient had the most intensive and widespread ^{131}I-mIBG uptake in our group reflecting increased NB load, which can explain her higher than expected radiation dose from the first ^{131}I-mIBG fraction. However, the patient tolerated the treatment well without any sustained haematological depression or other acute toxicities. For this patient the stem cell support was given

two weeks after the single dose, but effectively 2 weeks ahead of the scheduled time point in the protocol.

Patient 5 received lower whole-body dose than anticipated. The MATIN protocol is designed to give approximately 2 Gy whole-body dose in each fraction. To follow the protocol accordingly, ~50 GBq ^{131}I-mIBG should have been given to Patient 5 in round 2. However, due to radiation safety concerns and the fact that the patient had haematological aplasia at the time of admission for the second course of 131I-mIBG treatment, a decision was made to replicate the administered activity values from the first course. To the best of our knowledge, no such high activity single dose of ^{131}I-mIBG (~50 GBq) has been previously reported in the literature [6,13,14]. The patient had the most sustained haematological aplasia following treatment in our patient group and is the only one without ^{123}I-mIBG uptake on later diagnostic scans.

Even though the expected target radiation dose for two out of five patients deviated from 4 Gy, five patients do not provide enough experience to alter the dose-regimen defined by the MATIN protocol. However, in the future, we will consider reducing the first fraction (<444 MBq/kg) slightly if a patient has a very high mIBG retention as seen on the ^{123}I-mIBG scans. Our limited experiences confirm the strategy of dividing the ^{131}I-mIBG administration in two fractions to avoid over-dosage and excessive toxicity.

Ideally, optimal *in vivo* dosimetry includes calculations of dose to target and/or maximum tolerable dose to normal tissue. Such calculations require accurate quantitative imaging of ^{131}I-mIBG distribution at numerous time points after administration. However, there are challenges associated with image quantification, and limited evidence of the relationship between administered activity, tumour-absorbed dose and response. The use of whole-body dosimetry facilitates a simple and standardized approach of increasing administered activity while controlling toxicity.

Radiation protection and exposure

^{131}I-mIBG treatment of children with high-risk NB requires that family caregivers are exposed to gamma radiation. The family members were the main caregivers during hospitalization, and they were also successfully conducting the dose rate measurements. All caregivers received training by medical physicists in general radiation safety principles, and they were closely monitored with personal dosimeters. The presence of a medical physicist during the whole period of hospitalization was important to provide support and supervision. Before treatment, the families were encouraged to bring as many caregivers as possible in order to distribute and reduce the time spent with the patient in the isolation unit. As expected, the caregivers for the youngest children received a significantly higher dose than the caregivers for the oldest (>6 years), mainly due to changing of diapers, breastfeeding and nurturing. Those older than 6 years required less direct care, and spent most of the time at a larger distance from their caregivers. Therefore, the younger the child, the more need for several caregivers. The radiation doses to the caregivers included in this report ranged from 0.1 to 8.0 mSv (Table 2), and even though all caregivers for the youngest children (<3 years) received radiation doses ≥3 mSv, our results were in compliance with international and national guidelines for caregivers involved in radionuclide therapy [8]. The guidelines state that the given dose constraints (adults >60 years: 15 mSv; adults <60 years: 3 mSv) are not expected to be applied to family and close friends comforting children with neuroblastoma during 131I-mIBG treatment. Even so, a useful strategy particularly when treating the youngest patients, is to involve older adult caregivers. Our results are in agreement with previous published literature [15,16], reporting that caregiver radiation exposure doses ranged from 0-5 mSv.

Additional risk for radiation-induced cancer for family caregivers involved in ^{131}I-mIBG treatment is low. The maximum radiation dose to caregivers in this study was 8 mSv, which equals twice the annual natural background radiation in Norway. Based on a conservative risk assessment published by the Committee on the Biological Effects of Ionizing Radiation [17], 8 mSv corresponds to an additional risk of 0.05% and 0.02% for a 50-year and a 70-year old person, respectively. In addition, the maximal received radiation dose for caregivers is significantly below the occupational threshold of 20 mSv/year, which is the dose considered as acceptable risk for workers. Even so, a useful strategy particularly when treating the youngest patients, is to involve older adult caregivers.

The hospital staff involved in ^{131}I-mIBG treatment also received radiation safety training and were monitored by electronic personal dosimeters. The paediatric nurses and doctors are currently not included in the national personal dosimetry monitoring system, which is required for personal likely to receive a radiation dose of >1 mSv/year. Our recordings showed that the radiation exposure to the hospital staff was low, and significantly less than 1 mSv per ^{131}I-mIBG treatment. Hence, no additional measures are required. However, if the frequency of ^{131}I-mIBG treatment increases, this might involve redefining this group of staff as occupationally exposed personnel (i.e. dose constraint 20 mSv).

Conclusion

131I-mIBG treatment for children with neuroblastoma has been successfully established at our institution. Radiation doses to caregivers and hospital staff have been acceptable and in compliance with national and international guidelines. Two out of five patients deviated from the anticipated dose exposure defined by the MATIN protocol. Hence, dosimetry-guidance during administration of high dose ^{131}I-mIBG treatment is beneficial and necessary.

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