Biodistribution of Post-Therapeutic Versus Diagnostic 
\(^{131}\)I-MIBG Scans in Children With Neuroblastoma

Marc P. Hickeson, MD, Martin Charron, MD,* John M. Maris, MD, Patricia Brophy, CRNP, Tammy I. Kang, MD, Hongming Zhuang, MD, PhD, Jehanzeb Khan, MD, and Teresa Nevrotski, CNMT

INTRODUCTION

Neuroblastoma is the most commonly diagnosed extracranial solid pediatric malignancy in the first year of life [1]. It represents 7% of all pediatric cancers and is the cause of 15% of all childhood cancer deaths [2]. There are 8.7 new cases per million children or 500–600 new cases annually in the US [1]. Neuroblastoma arises from neural crest derived sympathetic nervous system precursor cells. It is a clinically heterogeneous disease with patient outcome tightly correlated with patient age at diagnosis, local and metastatic extent of disease, and tumor biologic features such as the presence or absence of the n-myc oncogene amplification. At diagnosis, metastatic disease is identified in half of infants and in two thirds of children aged 1 year and older [3]. The most common sites of metastases are cortical bone and bone marrow as well as both regional and distant lymph nodes. Infants often show disease dissemination to the liver and subcutaneous tissues.

The diagnostic modalities that are used for determining the disease extent include bone marrow aspirates and biopsies, CT scan, MRI, \(^{99m}\)Tc-MDP bone scan, and \(^{131}\)I-MIBG or \(^{123}\)I-MIBG scan [2]. The sensitivity and specificity of MIBG are very high because most neuroblastomas take up MIBG [4].

The treatment of neuroblastoma depends on a risk category assignment that is based on the analysis of host of patient-specific and tumor-specific variables. However, over 50% of patients are categorized as high-risk due mainly to widespread disseminated disease in patients older than 1 year at diagnosis. These patients receive aggressive multimodal treatment including chemotherapy, radiation therapy, surgery, myeloablative chemotherapy followed by stem cell rescue, and biologic response modifiers [5]. Despite this, the long-term prognosis of advanced neuroblastoma remains poor with current survival probabilities of less than 30%.

Since \(^{131}\)I-MIBG concentrates in neuroblastoma tumors, it is potentially capable of selectively delivering a substantial radiation dose to the neuroblastoma cells in both primary tumors and metastases [4]. \(^{131}\)I-MIBG therapy has been used in children with neuroblastoma who were resistant to conventional therapy and, more recently, as front line therapy with promising results [4–13].

There is however some evidence that some metastases that may be too small or too defective in trapping MIBG
to be visualized on the DS may be visualized when the patient returns for imaging a few days after the treatment dose of MIBG [14,15]. Recently, Fatourechi et al. reported abnormal $^{131}$I uptake in 13% of patients with differentiated thyroid cancer on the PTS in areas that were not seen on the DS [16]. The purpose of this study is to compare the difference in the biodistribution and sensitivity in the detection of metastatic disease with the DS and the PTS using $^{131}$I-MIBG in patients with neuroblastomas. The difference of the biodistribution of diagnostic and therapeutic $^{131}$I-MIBG and the sensitivity for the detection of metastatic disease have not been analyzed simultaneously on any study.

MATERIALS AND METHODS

Patients

Twenty-four patients: 10 males and 14 females aged 1.5–22.0 years (mean 8.9 years) were treated with $^{131}$I-MIBG over a period of 13 years. Twenty three patients had neuroblastoma and one had pheochromocytoma. Eighteen of these patients with neuroblastoma had $^{131}$I-MIBG DS performed in our institution and these were compared with their corresponding $^{131}$I-PTS. Out of these 18 patients, two had two pairs of DS and PTS and one had three pairs of DS and PTS. The total of pairs of DS and PTS was 22. Institutional Review Board approval was obtained for this retrospective study.

Imaging Protocols

For the DS, all patients were treated with SSKI on an adult dose of three drops daily beginning 1 day before the radiopharmaceutical injection and continuing for 6 days after tracer administration. The dose of $^{131}$I-MIBG was 37 MBq/1.73 m² (range: 2.6–44.4 MBq, mean: 17.8 MBq). Imaging was performed with a high-energy collimator at 48 hr after injection at 15 min per image. All images contained $256 \times 256$ pixels.

For the PTS, all patients were treated with SSKI on an adult dose of three drops daily starting 1 day before and ending 6 weeks after radiopharmaceutical administration. They were also given an anti-emetic about 1 hr prior to the therapeutic dose. The dose administered (range: 2.0–33.1 GBq, mean: 7.8 GBq) was determined either by dosimetry using a tracer dose of $^{131}$I-MIBG or by fixed dose of 444–666 MBq/kg depending on the phase of the trial. The therapeutic radiopharmaceutical was delivered from Ann Arbor, Michigan in the frozen state. After thawing, the prescribed dose was drawn up in a 60 ml syringe and diluted with normal saline to total volume of 30 ml. The shielded syringe was delivered to the patient’s room. It was then placed in a Medfusion 2010 infusion pump, situated behind lead bricks, connected to the patient’s venous access line, and administered over 90 min. At the end of the infusion, a suitable saline flush was used to clear the line of residual radiopharmaceutical. After this time, the radiation level was monitored by radiation safety until it was less than 0.07 mSv/hr at 1 m at which time the patient was discharged. Prior to discharge, a total body scan was obtained with a high energy collimator at 2 min per image and $256 \times 256$ pixels per image.

The same fields of view were compared between the DS and PTS. A lesion independent of its size is considered as one diseased site (i.e., one large lesion and one small focus each count as one diseased site). If the PTS detected an extension of the activity demonstrated on the DS, this would not be considered as additional diseased site unless that the new site is not contiguous to that detected in the DS. Conversely, if the DS scan detected two lesions that appeared as one larger lesion on the PTS, then this lesion would have been considered as one diseased site on both the DS and the PTS. All studies were reviewed by two nuclear medicine physicians in consensus.

RESULTS

In terms of the biodistribution (Table I), the PTS demonstrated MIBG activity in the following regions not detected on the DS: nasal mucosa ($N = 11$), cerebellum ($N = 5$) (Fig. 1), central brain region ($N = 5$), adrenals ($N = 3$), spleen ($N = 3$), kidneys ($N = 3$), thyroid ($N = 2$), salivary glands ($N = 1$), lower halves of the lungs ($N = 1$), urinary bladder ($N = 1$), bowel ($N = 1$), and an incisional scar ($N = 1$). Conversely, the DS identified activity in the following regions not detected on the PTS: thorax ($N = 1$), heart ($N = 1$), kidneys ($N = 1$), and urinary bladder ($N = 1$). The uptake at all of these sites was considered as normal physiological distribution on the basis of the symmetry of uptake, similar site, and shape in different patients, and absence of any clinical manifestation of malignancy at these sites on follow up.

In terms of the sensitivity for detecting neoplastic disease, abnormal uptake was detected in all 22 of 22 PTS (100%) and compared to 21 of 22 DS (95%). The PTS demonstrated sites of disease that were not evident in the DS in 16 of 22 cases (73%) and increased the confidence in detecting an additional lesion in another patient (5%). Two hundred ten lesions were detected on the PTS as compared to 151 on the DS, which represents 59 out of 151 (39%) more lesions seen on the PTS. An example is shown in Figure 2. The PTS upstaged the disease in 1 case of 22 (5%) and increased the confidence in diagnosing stage 4 disease in another patient. In one case, no disease was demonstrated on the DS in a patient considered to be in complete remission, and the PTS scan showed abnormal uptake in the left humerus (Fig. 3). In the other case, a subtle lesion was seen in the liver on the DS that was definite on the PTS.
When correlating to the dose per weight for the DS, the PTS revealed greater disease burden (Table II) in all three of three patients (100%) as compared to DS with doses of less than 0.5 MBq/kg and upstage the disease in none of the patients. The PTS detected more sites of disease in 9 of 12 patients (75%) as compared to DS with a dose between 0.50 and 0.99 MBq/kg and upstaged in one case (9%). The PTS resulted in increased number of disease sites in four of seven patients (57%) than on the DS scans with doses of 1.0 MBq/kg or higher and increased the confidence in detecting an additional lesion and upstage to stage 4 disease in one of seven patients (14%). When correlating to the dose per weight for the PTS, greater disease burden was demonstrated in 4 of 5 patients (80%), 4 of 7 patients (57%), and 8 of 10 patients (80%) for doses of less than 200 MBq/kg, 200–349 MBq/kg, and 350 MBq/kg or higher, respectively, as compared to the DS. The PTS upstaged the disease in 1 of 10 patients (10%) with a dose of 350 MBq/kg and increased the confidence of diagnosing stage 4 disease in 1 of 7 patients (57%) with a dose between 200 and 249 MBq/kg.

DISCUSSION

\(^{131}\)I-MIBG is radioiodinated analogue of noradrenaline [17]. The chemical structure includes the benzyl...
portion of bretylium with the guanidine group of guanethidine. The cellular uptake of MIBG into adrenomedullary cells is similar to norepinephrine. It takes place by two mechanisms: uptake-1 and uptake-2 [2,12,18]. Uptake-1 is an active process by the noradrenaline transport transmembrane protein and is a high affinity, saturable, sodium, energy, and temperature-dependent process. In contrast, uptake-2 is a non-specific mechanism, presumed to be passive diffusion and energy independent and unsaturable at concentrations of at least 5 mM.

In this study, MIBG uptake was observed in several sites on the PTS not evident on the DS. As the plasma concentrations of MIBG is <0.1 mM in therapeutic doses of carrier-free 131I-MIBG, uptake-1 is the predominant mechanism of uptake [18]. However, uptake-2 becomes increasingly less negligible in terms of the contribution of MIBG uptake at higher doses in the PTS. The spleen, the nasal mucosa, and the adrenals are all very vascular structures. The MIBG activity in the central brain probably represents the locus ceruleus in the brain stem and this structure and the cerebellum both contain relatively high density of adrenergic neurons [19]. Other observers have also demonstrated MIBG activity in the lung on the PTS that was not seen on the DS [20]. Possible explanations for the uptake in structures only seen using high doses of MIBG are by three possible mechanisms: by higher count densities provided by PTS, depending on the perfusion, and by the second mechanism of MIBG uptake.

Treatment with 131I-MIBG has been used in children with neuroblastoma for palliative and, recently, curative purposes. According to the cumulative experience of several centers, the overall objective response rate is approximately 35% in patients with chemoresistant neuroblastoma after induction chemotherapy or at relapse [13]. There are currently four major methods for determining the therapeutic dose to be delivered: by dosimetry using a tracer dose of MIBG, by dose per body weight, by fixed dose, and by dose escalation in which hematopoietic tissue is harvested for bone marrow transplant [4]. In our institution, 131I-MIBG therapy is given to patients.
<table>
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<th>Dose on PTS (GBq)</th>
<th>Dose/Wt on PTS (MBq/kg)</th>
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who are categorized as high risk and are refractory to chemotherapy.

The PTS increased the estimated disease burden in 16 cases (73%) and detected 39% more lesions than the corresponding DS. The PTS upstaged one case and increased the confidence in diagnosing stage 4 disease in another in which a questionable lesion in the liver seen on the DS and was definite on the PTS. In the other case, the DS scan demonstrated an apparently complete response to chemotherapy with no active lesions seen; however, a lesion in the left humerus was seen on the PTS. Since the PTS detects more diseased sites than the DS, assessing treatment response from a therapeutic dose of $^{131}$I-MIBG with the DS is difficult. The increase of number of lesions seen on the PTS is thought to be due to the high activity of $^{131}$I-MIBG providing higher count densities and, consequently, higher lesion’s signal to background ratios than seen on the DS. Parisi et al. attributed the detectability of lesions as a function of contrast and spatial frequency composition [15]. This study also reported a greater sensitivity of the $^{131}$I-MIBG PTS as compared to the DS in 14 patients [15]. Similar conclusions were observed with $^{131}$I scanning using diagnostic and therapeutic doses for differentiated thyroid cancer for similar reasons [21–23]. It would also be interesting to compare the sensitivity of detection of metastatic lesions with $^{123}$I-MIBG scintigraphy and with the $^{131}$I-MIBG PTS. The diagnostic scans (DS) with $^{123}$I-MIBG probably provide higher sensitivity for disease detection and lower radiation doses to patients than with those using $^{131}$I-MIBG. However, a correlation to the dose with the sensitivity cannot be determined on this study when analyzing the DS or the PTS individually.

The limitations of this study are the lack of tissue biopsy for confirmation and the lack of perfect method in quantifying the number of diseased sites. MIBG uptake has been previously described in the salivary glands, thyroid (likely due to free iodine), heart, spleen, bowel, kidney, and bladder [24]. Fortunately, the other MIBG-avid tumors [25–34] are relatively uncommon in children, which explain the high positive predictive value of focal MIBG uptake for neuroblastoma in children. In addition, the sites of physiologic uptake were confirmed with the absence of any manifestation of malignancy on clinical follow up. The gold standard considered on this study was the number of individual sites demonstrated on the PTS. The method we adopted to determine the disease burden was to count the number of diseased sites observed on the DS scan and the PTS. Because the size of the lesions was not considered for disease involvement, this is not a perfectly accurate method to determine the disease burden. It is, however, a relatively reproducible method to compare the disease extent between the DS and the PTS.

MIBG scintigraphy remains the most sensitive modality for the detection of neuroblastoma. However, a small percentage of neuroblastoma lesions demonstrate a lack of avidity to MIBG. Biasotti et al. reported a 8% false negative rate in all patients with neuroblastoma [35]. If children with stages 1 or 2 disease only are considered, the false-positive rate was as high as 24%. This lack of avidity can be indicative of highly anaplastic neuroblastomas or in more mature neoplasms such as ganglioneuromas [36]. If lesions not avid to MIBG are present, then therapy with $^{131}$I-MIBG will not be helpful and the patient will be spared from having futile therapy.

CONCLUSIONS

All patients were treated as inpatient with $^{131}$I-MIBG. For this reason, they are readily accessible to return for imaging. Scanning after therapy does not pose any additional radiation risks. The PTS increases the confidence of detecting lesions seen on the DS as well as the number of lesions detected and may upstage the disease in a small number of patients. The biodistribution of MIBG is different using therapeutic doses as compared to the diagnostic doses and the PTS greatly improved the precision for detecting extent of disseminated disease.

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REFERENCES


