Chapter 3

I-131 Metaiodobenzylguanidine Therapy of Neuroectodermal Tumors

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Abstract

I-131 metaiodobenzylguanidine (MIBG) is a noradrenaline analogue and acts as an adrenergic neuron blocker. It is commonly used in the radionuclide treatment of neuroectodermal-derived tumors (Stage III–IV neuroblastoma, inoperable pheochromocytoma, paraganglioma and carcinoid tumor, metastatic or recurrent medullary thyroid cancer). These are rare tumors and clinical data about therapeutic options accumulate slowly. I-131 MIBG has a well-known role in the salvage therapy of these tumors; however, recent data suggest that it may also be beneficial to use as the first-line method. Here, we define characteristics of the radiopharmaceutical, mention cautions during administration and discuss clinical applications of I-131 MIBG therapy of the neuroectodermal tumors.

Keywords: iodobenzylguanidine, neuroectodermal tumors, therapeutics, neoplasms, radiation

1. Introduction

Metaiodobenzylguanidine (MIBG, Iobenguane) is an aralkylguanidine analogue, composed of bretylium and guanethidine (an adrenergic neuron blocker). It acts as a noradrenaline analogue and is taken up by adrenergic sympathetically innervated tissues. Neural crest originated tumors, which are derived from sympathetic nervous system, are therefore suitable for scintigraphic imaging and targeted therapy with radioiodine-labeled MIBG. I-131-labeled MIBG is the compound used for therapy in neuroectodermal tumors. These tumors have a very low incidence, and thus clinical experience in therapy with I-131 MIBG is limited to specific reference centers. This chapter aims to give information about the physical characteristics of I-131 MIBG, uptake mechanisms of the radiocompound in the tumoral

tissue, indications and contraindications for I-131 MIBG therapy, specifications for the facility where the therapy will be performed, patient preparation and administration of I-131 MIBG, follow-up and precautions on possible side effects and make an overview on the clinical studies about I-131 MIBG therapy.

2. Radiopharmaceutical

I-131 MIBG is a "theranostic," the term that stands for the agents used for both diagnostic and therapeutic approach [1]. Physical properties of I-131 bring in this advantage. I-131 has a gamma ray at 364 keV and a mean beta emission of 606 keV. Beta particular emission causes cell death, and gamma rays are used for scintigraphic imaging. A half-life of 8.02 days provides enough time for labeling and shipping [2].

Metaiodobenzylguanidine (MIBG) is a synthetic analogue of norepinephrine and an aralkylguanidine, a combination of benzyl group of bretylium and guanidine group of guanethidine [3]. The reason why MIBG is the preferred pharmaceutical among other aralkylguanidines is that it shows the lowest liver uptake, the best in vivo stability, and thus, lowest amount of free radioiodine is trapped by thyroid tissue. In a study by Wieland et al., 100 μCi I-125-labeled iodobenzylguanidine isomers (para, ortho and meta) were intravenously administered to 41 mongrel dogs separately. Following injections, tissue distribution of each isomer in a given time was detected by obtaining samples from 18 different tissues. They found out that meta and para isomers were taken up by adrenal medulla starting from 2 h of injection and lasted till 8 days. Despite adrenal medulla is surrounded by liver, an organ with metabolic activity and adrenergic innervation, even on the measurements, performed on 5 days of injection, the ratio of adrenal medulla counts/liver counts was calculated as high as 1000. In addition to adrenal medulla, high amount of radiopharmaceutical uptake was detected in thyroid. However, detailed analysis of thyroid tissue measurements revealed that meta-isomer was more resistant to in vivo deiodination [4].

I-131 MIBG is rapidly cleared from bloodstream following intravenous administration and taken up by adrenergically innervated tissues like adrenal medulla, heart and salivary glands. In the first hour, heart and lungs are major apparent organs. Maximal uptake in the tumoral tissue occurs 24–96 h later. The major route of elimination of the radiopharmaceutical is glomerular filtration. In subject with normal renal function, 50% of the administered activity was shown to be excreted unchanged via urine in 24 h and 90% is eliminated by the kidneys in 4 days. A very small amount of I-131 MIBG is metabolized in vivo (<10%). End products are m-iodohippuric acid, m-iodobenzoic acid, 4-hydroxy-3-iodobenzylguanidine and free radioiodine [5, 6].

Norepinephrine (NE) is synthesized by dopamine-hydroxylase from dopamine (DA) in presynaptic neurons of adrenal medulla, carried by the vesicles and secreted to the synaptic gap. NE then binds to pre- and postsynaptic adrenergic receptors in the synaptic gap. NE is reuptaken by the pre- and postsynaptic cells through NE transporters (NETs) and stored in the vesicles. This reuptake process is called "specific neuronal uptake 1" and is Na and

energy (ATP) dependant. Ligand affinity is high, whereas saturability is low. It is sensitive to heat and ouabaine, Na+/K+/ATP'ase inhibitor. MIBG, the Ne analogue, acts similar to NE. As the molecular structure remains unchanged, I-131-labeled MIBG is also taken up by the NET expressing cells (mainly derived from the neural crest), using NETs. However, this specific mechanism of uptake is not the only uptake mechanism of I-131 MIBG uptake in cellular level. The second mechanism is nonspecific passive diffusion, which takes place in all cell types. Specific neuronal uptake is 50 times more effective than passive diffusion [4, 7, 8]. After internalized in the cell, I-131 MIBG is taken up by vesicular monoamine transporters (VMAT 1 and 2) and stored in neurosecretory granules [9].

3. Indications

Although any tumor capable of I-131 uptake on pretherapy I-131 MIBG scan may have a chance to be treated with I-131 MIBG, I-131 MIBG has a well-established place only in therapy regimen of some common neuroendocrine tumors: Stage III–IV neuroblastoma (NB), inoperable pheochromocytoma, paraganglioma and carcinoid tumor, metastatic or recurrent medullary thyroid cancer [10]. To decide whether a neuroendocrine tumor patient is eligible to I-131 MIBG therapy, I-131 MIBG avidity should be concerned first. This decision can be made either visually (lesions detectable above background activity on I-123 or I-131 MIBG scan) or semiquantitatively (like target/background >2, or >1% of the injected activity taken up by the tumor) [11–16].

4. Contraindications

Absolute contraindications for I-131 MIBG therapy are given as pregnancy and breast feeding. If life expectancy is less than 3 months, therapy is not recommended except for those given for pain palliation. Renal insufficiency is also an undesirable condition for I-131MIBG therapy. Relative contraindications include inconvenient isolation conditions, urinary incontinence, progressive deterioration in renal functions (GFR < 30 ml/min) and myelotoxicity (WBC < 3.0×10^9/l, PLT < 100×10^9/l). Patients susceptible to toxicities should be followed up closely and activity reduction should be concerned [10].

5. Protocol

5.1. Patient preparation

5.1.1. Eligibility for I-131 MIBG therapy

Patients should be evaluated with I-131 or I-123 MIBG scan before therapy to make sure that the tumoral lesions are I-131 MIBG avid [17].

5.1.2. Thyroid blockade

Unbound or in vivo radiolyzed free radioiodine is taken up by the thyroid and may cause destruction. Thyroidal uptake should be inhibited by oral stable iodine. Oral iodine (16–130 mg/day) or potassium perchlorate capsules (100–400 m/day) can be used, although iodine capsules are more preferred in pediatric patients because of its better taste. Lugol solution is a simpler alternative, administered 1 drop/kg/day with a maximum of 40 (20 drops twice a day). The treatment should begin 48–24 h before I-131 MIBG administration and continued for 10–15 days after therapy [10].

5.1.3. Drug interactions

Various drugs interfere with I-131 MIBG uptake in the target tissue. Drug groups and recommended withdrawal times are presented in **Table 1**. They may inhibit Na-dependent uptake to cell, intracellular vesicular uptake, depletion of I-131 MIBG from the granules, Ca-mediated uptake and some other unproven pathways [10].

Neuroendocrine tumors, especially PHEO and paragangliomas (PGLs), present with hypertension and tachycardia due to secreted catecholamines. Management includes alpha and beta blockers. Discontinuation of these drugs is needed before I-131 MIBG therapy. This causes

Group	Recommended withdrawal time
Antiarrhythmics (amiodaron)	Not practical
Combined alpha-beta blockers (labetolol)	72 h
Adrenergic neuron blockers	48 h
Alpha blockers	15 days
Calcium channel blockers	24–48 h
Inotropic sympathomimetics	24 h
Vasoconstrictor sympathomimetics	24 h
B2 stimulants	24 h
Other adrenoreceptor stimulants (Orciprenaline)	24 h
Systemic and nasal decongestants, cough and cold preparations	24–48 h
Sympathomimetics for glaucoma	48 h
Antipsychotics	24 h–15 days
Sedatizing antihistaminics	24 h
Opioid analgesic drugs	24 h
Tricyclic antidepressants	24–48 h
Tricyclic-related antidepressants	48 h–3 days
CNS stimulants	24 h–5 days

Table 1. Drug groups which may interfere with I-131 MIBG uptake and recommended withdrawal time.

an interruption in symptomatic management. Alpha blocker phenoxybenzamine and beta blocker atenolole do not interfere with I-131 MIBG uptake. Among calcium channel blockers, nifedipine is a safe option, as interference has not been reported [18].

5.2. Dose administration

The radiopharmaceutical administration can be performed either in or outpatient, according to the amount of activity administered and local radiation protection rules. If performed in-patient, dose administration should be performed in an approved nuclear medicine facility with appropriately shielded rooms, radiation safety equipment and capability of management in case of contamination. Dose administration should be supervised by an authorized person, that is, according to the most local commissions, a nuclear medicine specialist [10].

I-131 MIBG is injected intravenously by slow infusion over 1–2 h in a lead shielded infusion set [10, 19, 20]. Possible side effects caused by cold MIBG are aimed to be avoided by slow infusion. It has been stated that I-131 MIBG at high specific activity has a lower potential to cause side effects and thus can be infused in a shorter time period [21].

Vital signs should be closely monitored during and after I-131 MIBG infusion. Short-acting alpha and beta blockers should be kept ready during and after infusion in case sympathetic discharge symptoms occur. I-131 MIBG infusion can be slowed down or stopped if hypertension is unstable [10].

5.3. Determination of activity

Empirical fixed dose, fixed activity per body weight or dosimetrically estimated doses can be given. Single administered activities range between 100 and 300 mCi (3.7–11.2 GBq). Dosimetric calculation is based on dose-limiting side effect, myelotoxicity. Activities delivering 2–4 Gy dose to blood are calculated. Much higher doses than fixed doses can be given by dosimetric approach [22].

In case of repeat administrations, therapy response and toxicities should be taken in consideration to decide which dose to be given. Dose reduction would be appropriate in case of hematologic or renal insufficiency [10]

6. Clinical manifestations

6.1. Neuroblastoma

Neuroblastoma (NB) is the most frequent extracranial tumor of childhood (constituting 8–10% of the pediatric tumors) and presents with metastatic disease in almost half of the cases. Originating from the neural crest, NB can be found anywhere in the sympathetic ganglion chain but mostly in the adrenal gland [23]. Because of the fact that neuroblastomas show high affinity for I-131 MIBG (>90%), I-131 MIBG therapy is of clinical interest for selective internal radiotherapy of NB [10, 24].

Historically, I-131 MIBG was first tried in refractory or relapsed NB patients. Early Phase I dose escalation studies investigated I-131 MIBG as a single agent in the therapy of refractory neuroblastoma. Several dose regimens have been tried by different investigators, yielding a wide range of complete and partial response (CR and PR): 0–66% [25–35]. Weight-based dose arrangement is now well established. 2–6 mCi (74–222 MBq)/kg cause mild hematological side effects but does not provide a high antitumor efficacy either. Significant antitumoral effects start at doses over >6 mCi(222 MBq)/kg [36]. However, the degree of bone marrow depression increases by rising doses, and a new approach was developed combining higher effective doses with prior cryopreservation of stem cells and bone marrow transplantation following I-131 MIBG therapy. Greater than 12 mCi (444 MBq)/kg is the settled limit for stem cell rescue [37]. Doses above 15 mCi (555 MBq)/kg are now used for myeloablation either with or without myeloablative chemotherapies [36]. Matthay et al. have published a large trial of I-131 MIBG monotherapy in refractory or relapsed NB. The vast majority of the patient group received 18 mCi (666 MBq)/kg I-131 MIBG, whereas others were given 12 mCi (444 MBq)/kg. Overall CR and PR rates were found 36%. However, investigators also revealed that age, site of disease involvement, previously received therapies and time between first diagnosis and first I-131 MIBG dose are important in prediction of treatment success. Response rates were 55 and 40% above and below age 12, respectively. Soft tissue, skeletal and bone marrow involvement responded in 50, 45 and 26%, respectively. Event-free survival rate was found 18%, and 2-year overall survival was 29%. Together with hematologic toxicity, to a lesser extent, other side effects such as hepatic, pulmonary and infectious toxicities and febrile neutropenia were also reported in this study [38].

I-131 MIBG monotherapy is also combined with myeloablative chemotherapies to be used in higher doses with stem cell rescue. A leading study by Yanik et al. suggested that carboplatine-etoposide-melphelan in combination with I-131 MIBG therapy administered in 12 mCi (444 MBq)/kg doses in 12 patients. Therapy was well tolerated and 5/8 patients with metastatic disease showed complete and 2/8 showed partial response [39]. In a larger cohort group, 3-year event-free survival and overall survival rates were found 38 and 20% in patients who had a PR to induction therapy and 20 and 62% in patients who had a progressive disease [40]. It was also reported that I-131 MIBG was not detrimental to hematologic recovery after stem cell transplantation [41].

In 2000s, in relapsed or refractory NB patients, tandem doses of I-131 MIBG infusions were tried. The best therapy responses were achieved after initial dose administration and response rates decreased by repeat infusions. That was also true for patients who have already received myeloablative doses of I-131 MIBG (>18 Mci(666 MBq)/kg) [42–44]. Although well tolerated, overall clinical response rates in a meta-analysis were reported as 30%, even in tandem infusions [45]. This leads the investigators to seek for other strategies to increase the efficacy of I-131 MIBG therapy. NET expression increase would be very beneficial to increase I-131 MIBG uptake by the tumor cells. Among the chemotherapeuticals, cisplatin and topotecan are agents of choice to augment NET expression. While response rates were ameliorated, side effects were not significantly aggravated [46, 47]. In a study of refractory NB patients who received 200 mCi (7.4 GBq) I-131 MIBG in combination with cisplatin, cyclophosphamide (plus etoposide and vincristine or not), an overall response rate of 75% was achieved [46].

Promising results experienced over years with I-131 MIBG therapy have lead to a new approach, usage of I-131 MIBG in the front-line as a part of the induction therapy for patients who do not have a relapsed or refractory tumor yet. Investigators have found that I-131 MIBG avid tumors, which are not exposed to chemo-radiotherapies yet, are more responsive to I-131 MIBG therapy given at the early steps of the therapy algorithm. In the preoperative period, I-131 MIBG therapy performed at diagnosis was reported to lead to a response rate of over 70%, which is obviously higher than the rates obtained after conventional therapies [48]. De Kraker et al. proposed three major arguments: First, if performed before surgery, I-131 MIBG reduced the volume of the primary and metastatic tumors. Second, overlapping toxic situations confronted with chemotherapy in combination therapies are avoided. Finally, cross-fire effect achieved at the first-line therapy, the ability of the radiation dose given to a tumor cell also causes death of the neighboring cells. The authors published the largest study in this field with 44 high-risk patients who received two cycles of I-131 MIBG as an induction therapy and received a response rate of 73% [49]. Bleeker et al. have also reported that together with high success rates, side effects were also lower [50]. Combination of I-131 MIBG with chemotherapeuticals did not cause a significant increase in side effects [50, 51].

Pain palliation with I-131 MIBG is another secondary benefit reported commonly in NB [31]. Low dose (5 mCi (185 MBq)/kg) I-131 MIBG has also been suggested as an effective means for pain palliation in metastatic disease [52].

6.2. Pheochromocytoma and paraganglioma

Paragangliomas (PGL) arise from sympathetic chromaffin tissue (adrenal or extraadrenal) and parasympathetic ganglions of the head and neck. Pheochromocytomas (PCC), which originate from the adrenal medulla, constitute 80% of all paragangliomas (PG) [53, 54]. Most PGLs are benign, while about 10% of PCCs and 10–20% of extraadrenal non-head and neck PGLs may undergo malignant degeneration [55]. Malignant disease refers to existence of metastatic lesions where neuroendocrine tissue is not expected to exist [56–58]. In malignant PCC/PGL, malignant disease has a bad prognosis and together with palliative therapy, I-131 MIBG has been tried [59, 60].

I-131 MIBG was first tried by Sission et al. on MIBG avid PCC patients. Fractionated doses of a total of 373–484 mCi (13.8–17.9 GBq) I-131 MIBG was given to five patients and two patients responded partially. Hormone secretion was decreased and tumor volume declined by more than 50% in these patients [37, 61]. Many other series with larger number of patients came afterwards. However, it is hard to make a final conclusion about the effectiveness of I-131 MIBG therapy on PCC/PGLs because these studies differed in many ways. First of all, as PCC/PGLs are relatively rare tumors, study populations were small and heterogenous in many studies. Patient selection criteria for I-131 MIBG therapy varied. Some administered I-131 MIBG therapy only in progressive cases, while in some studies patients with stable disease were also included. In stable cases, stability may not be totally attributable to the effectiveness of I-131 MIBG therapy, as these patients may already have stayed progress free even if no additional therapies were given. The amount of activity, dose fractionation, time elapsed between two therapy sessions, tumor response and hormonal response evaluation criteria were all set

differently in these cohorts. Moreover, PCC and PGLs may respond differently to I-131 MIBG therapy, and separate analysis of them could give more accurate and realistic results.

In the literature, generally low (64–200 mCi) (2.368–7.4 GBq), intermediate (200–500 mCi) (7.4–18.5 MBq) and high (1.2–1.8 mCi) (444–666 GBq) doses of I-131 MIBG with stem cell support have been tried. Low and intermediate doses were chosen in order to be able to give repeat doses and thus decrease toxicities. Tandem doses resulted in cumulative doses as high as 2.3 Ci (85.1 MBq), but usually in a range of 500–1000 mCi (18.5–37 MBq). A review analyzing the results of repeat low dose I-131 MIBG, CR, PR, SD and PD rates were found 4, 26, 50 and 13%, respectively. Objective hormonal response was obtained completely in 13% and partially in 32%. Symptomatic relief due to hormonal excess was maintained in 76% of the patients [62]. Comparison of three methodologies was reported in 33 patients. Median survival was 4.7 years for patients responding to I-131 MIBG therapy and 1.7 years for nonresponders. Patients who received high doses (>500 mCi) (>18.5 MBq) had a higher survival rate than the low dose group (3.8 versus 2.6 years) [63]. A recent meta-analysis by Hulsteijn et al. aimed to present effectiveness of I-131 MIBG therapy in malignant PCC/PGL. If effects on tumor volume are considered, pooled proportions of CR, PR and SD were found to be 0.03, 0.27 and 0.52, respectively. Hormonal response rates were 0.11, 0.4 and 0.21, respectively. Five-year survival rates ranged between 45 and 64% and PFSs were 23.1–28.5 months. A separate analysis revealed better hormonal response in PGL than PCC [64].

6.3. Others

The use of I-131 MIBG in carcinoid tumors and medullary thyroid carcinoma has been reported in relapse or refractory cases. Certain eligibility criterion is of course I-131 MIBG avidity proven by I-123 MIBG scan. I-131 MIBG therapy in these patients is rather palliative and aims to increase quality of life. Medullary thyroid carcinoma is rare and only about 34% of medullary thyroid cancer patients have an I-131 MIBG avidity; thus, the experience in this field is quite limited [24, 65–67]. In a study by Safford et al., a relatively wider group of patients with metastatic carcinoid tumor were given 77–1076 mCi (2.849–39.812 GBq) (mean 400 mCi) (mean 14.8 GBq) I-131 MIBG in 1–3 fractions. Symptomatic relief was gained in about half of the patients (49%). However, only 15% of them showed tumor volume decrease, and no significant effect on survival was reported [68].

7. Toxicity

Early side effects of I-131 MIBG therapy occur in the first hours or days of treatment. Nausea and vomiting are common side effects caused by acute radiation gastritis. Antiemetics are routinely recommended before the infusion starts. Its incidence has been reported between 4 and 40% [20, 69–73]. During I-131 MIBG infusion, catecholamine discharge may cause hypertension and tachycardia in 20% of the patients [11]. Although slow infusion and high specific activity preparations may decrease probability, alpha and beta blockers should be prepared to be used in case of emergency. Acute parotitis can be caused by I-131 MIBG uptake in the salivary glands. Anti-inflammatory agents may help symptomatic relief. Chronic xerostomia has not been reported yet [74].

The most important subacute toxicity is hematotoxicity. Bone marrow is the dose-limiting organ for I-131 MIBG therapy. Because I-131 MIBG binds to platelets, thrombocytopenia is usually more apparent than leucopenia. Hematotoxicity is dose dependent. Doses above 12 mCi(444 MBq)/kg have been shown to cause severe bone marrow toxicity, and in cases of doses exceeding 15 mCi(555 MBq)/kg or repeat doses, stem cell support is required [24, 75, 76].

Late complications of I-131 MIBG include hypothyroidism and secondary malignancies. Hypothyroidism is a result of destruction caused by free radioiodine existing in the product or released after I-131 is metabolized. It is seen months or years after therapy in about 7–12% of the patients [77–81]. This is why thyroid blocking is essential during therapy.

Secondary malignancies such as myelodisplastic syndrome (MDS) and acute myelogenous leukemia (AML) have been reported in about 2–4% of patients [82–84]. As these patients are treated with chemo-radiotherapies in combination with I-131 MIBG, the contribution of I-131 MIBG alone to secondary malignancy development is a matter of debate. Alkylator-based chemotherapeuticals and external radiotherapy are also responsible for mutagenic effects [85].

Other side effects of I-131 MIBG such as pulmonary, cardiac and neurologic complications are rare. However, as liver shows high I-131 MIBG uptake, hepatotoxicity may become clinically evident at high doses. However, this effect is usually transient and aggravated by combination chemo-radiotherapies [81, 86]. Hypogonadism has been reported in higher frequencies with higher I-131 MIBG doses [11, 73, 87].

8. Noncarrier-added I-131 MIBG: an attempt to increase therapy efficiency

I-131 MIBG is synthesized from I-127 MIBG (cold MIBG) by substituting stable iodine by radioiodine [88]. The end product contains I-131 MIBG/I-127 MIBG ratio of 1:2000 [89]. This impurity causes a competition of I-131 and I-127 MIBG for NET and heterogenous tumoral uptake of I-131 MIBG, leaving a considerable amount of tumor cells nonirradiated. Excess MIBG, by the way, can cause symptoms due to sympathetic discharge. Non-carrier added I-131 MIBG was developed both to increase efficiency and to decrease side effects [90]. Noncarrier-added I-131 MIBG will probably be a favorable alternative form after toxicity, and dose escalation studies are completed [91].

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