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Review Article

I-131-MIBG therapies

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ABSTRACT

Metaiodobenzylguanidine (MIBG) is a tracer that selectively targets neuroendocrine cells. On this basis, radiolabeled iodinated-MIBG (I-131-MIBG) has been introduced as a molecular nuclear therapy in the management of neuroendocrine tumors, including neuroblastoma, pheochromocytoma, paraganglioma, neuroendocrine carcinomas, and other rare neuroendocrine tumors. Extensive work has been addressed to develop I-131-MIBG therapy: doses, therapeutic schemes, and efficiency. In this paper, we present an overview on I-131-MIBG therapy, with main focus on different aspects how to perform this treatment.

1. Introduction

Early studies in the 1970s identified a number of guanithidine derivates, including metaiodobenzylguanidine (MIBG). Due to its molecular analogy with norepinephrine, MIBG is taken up by neuroendocrine cells through an active mechanism leading to a specific concentration of the molecule within the cells. Early studies in the 1970s and 1980s demonstrated the effectiveness of MIBG to accumulate within the adrenal medullary tissue [1], as well as in its related neuroendocrine tumors [2]. On this basis, MIBG radiolabelled with iodine (as I-123 or I-131) was first introduced as a molecular imaging agent. Subsequently, on the same basis, iodine-radiolabelled MIBG was proposed for therapeutic use of neuroendocrine tumors. In 1984, the first therapy with I-131-MIBG was described in patients with pheochromocytoma [3]. In the same period, the first reports appeared on the use of this radiopharmaceutical in patients with neuroblastoma [4] and neuroendocrine carcinomas [5].

Since that time many patients have been treated with I-131-MIBG. In Europe, it has been approved for therapeutic use and is widely available for clinical use, but less in the Unites States and Canada. A detailed guideline on the use of MIBG as a molecular nuclear therapeutic agent is available [6,7].

1.1. Neuroendocrine tumors

1.1.1. Neuroblastoma

Neuroblastoma, a tumor of the autonomic nervous system, is the most frequent extracranial solid tumor in childhood, accounting for 8–10% of all childhood malignancies. It is an embryonal malignancy arising from the sympathetic nervous system. Neuroblastoma occurs commonly in young children with 50% of them presenting before 2 years of age and more than 90% before 5 years of age [8–10]. There is a marked variability in the clinical behavior of neuroblastoma, ranging from spontaneous regression, differentiation into benign ganglioneuromas, to rapid and progressive fatal disease [10]. This variable natural history of neuroblastoma is linked to the age of presentation. Most infants younger than 12 months of age, even with metastatic disease, have a favorable outcome with chemotherapy and surgery [10–13]. In contrast, children older than 12 months of age represent the group with high-risk disease as they usually develop a poor response to therapy. Despite substantial progress in the understanding of the disease, the prognosis of these neuroblastoma patients remains poor. The 3-year progression-free survival in patients over 1 year who present metastatic disease remains less than 35% [8,10,11]. Patients who do not achieve a complete response to induction therapy and patients who relapse after a prior transplantation have a less than 20% event-free survival rate [14].

1.1.2. Neuroendocrine tumors in adults

1.1.2.1. Pheochromocytoma and paraganglioma. Pheochromocytomas arise from chromaffin cells of the adrenal gland and paragangliomas from chromaffin cells in extra-adrenal sympathetic nervous elements. These have an incidence of 0.1–0.8 per 100,000, of which only about 10% occur in childhood. They secrete cathecolamines, accounting for sustained or paroxysmal hypertension as the presenting sign in up to 80% of cases [12].

1.1.2.2. Medullary thyroid carcinomas. Medullary thyroid carcinomas arise from the parafollicular C-cells and account for 3–10% of all thyroid cancers. About one-third are familial, either in isolation or associated with MEN IIA and IIB. Medullary thyroid carcinomas present as a thyroid nodule or mass. As C-cells produce

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calcitonin, increase in calcitonin levels is a good marker of tumoral progression. However, as calcitonin does not cause any manifest clinical syndrome, medullary thyroid carcinomas usually remain clinically silent, even at advanced stages [12].

1.1.2.3. Neuroendocrine carcinomas. Neuroendocrine carcinomas arise from the enterochromaffin or Kulchitsky cells, which are found in the epithelia of diverse locations of the body. The incidence is 0.1–0.14 per 100,000. The hormone active tumors secrete a variety of vasoactive peptides responsible for the so-called carcinoid syndrome of flushing, diarrhea, bronchospasm, and endocardial fibrosis. Serotonin is a characteristic product, hence biochemical diagnosis is based on urinary levels of its metabolite, 5-hydroxy-indoleacetic acid (5-HIAA) [12].

1.2. MIBG

1.2.1. MIBG and (I-131)-MIBG uptake in the neuroendocrine cells

Early preclinical investigations observed that most of neuroblastoma cell lines demonstrate specific uptake of iodinated-MIBG. The molecule is likely to be taken up into the cells by the neuroepinephrine transporter, as the uptake is inhibited by norepinephrine, in a competitive manner [15]. Likewise, imipramine, an inhibitor of norepinephrine transport decreases significantly MIBG uptake in the cells [16]. In addition, MIBG uptake shows a strong correlation with norepinephrine transporter expression levels [17]. Neuroendocrine cells that do not actively take up MIBG become MIBG avid when transfected with the norepinephrine transporter gene [18]. These observations were confirmed also in the clinical setting. In a study of 54 neuroblastoma patients, most of the tumors that did not express the norepinephrine receptor, as shown by genetic and protein analysis, demonstrated no uptake of MIBG. Only in isolated cases, tumors that did not express norepinephrine receptor, showed MIBG uptake [17]. This could suggest an additional low-grade passive, non-receptor dependent diffusion of MIBG into the cells or intracellular uptake through other receptor systems as well.

Once taken up into the neuroblastoma cells, most MIBG appears to be stored in the cytoplasm and mitochondria, rather than in the neurosecretory granules that store norepinephrine [19,20].

Several additional factors have been found to modulate MIBG uptake by neuroendocrine tumor cells. Grade of malignancy is increasingly recognized as an important tumor feature in the MIBG therapy of the neuroendocrine tumors. For instance, low malignant/well-differentiated neuroendocrine carcinomas show a high MIBG uptake. In contrast, high-grade/poorly differentiated neuroendocrine carcinomas have a lower MIBG uptake capacity. There is a significant discrepancy with regard to MIBG affinity between the subtypes of neuroendocrine tumors, according to their ontogenetic origins. Nonpancreatic neuroendocrine tumors have a high MIBG affinity, in contrast to the poor MIBG uptake showed by the pancreatic tumors [21]. Hypoxic and moderate hyperthermic conditions were shown to reduce MIBG uptake, whereas oxygen i.e. a good tumor perfusion increases the MIBG uptake [20]. Pretreatment with interferon-alpha increases MIBG uptake as well [22]. Hydroxytyrosol, a naturally occurring compound with strong antioxidant properties, enhances norepinephrine transporter activity, suggesting that hydroxytyrosol may improve the effectiveness of MIBG uptake in the cells [23].

With regard to chemotherapy agents, experimental as well as clinical data showed that pretreatment with cisplatin and doxorubicin, two active agents that are used in the clinical treatment of neuroblastoma, significantly intensify MIBG uptake in the tumor cells [24,25]. This effect may be due to an increase in norepinephrine transporter gene and subsequent norepinephrine receptor expression during and after chemotherapy [24]. Topotecan is another chemotherapeutic agent used in treatment of neuroendocrine tumors. Experimental data showed that a combined chemo- and radionuclide treatment of topotecan together with I-131-MIBG produced a significant inhibition of the tumor cell growth, as both agents impaired DNA repair mechanism in the tumor cells [26,27]. These results provide the rationale for use of some of the combination approaches in the clinical setting.

1.2.2. Pharmacokinetics of I-131-MIBG

There is limited data in the literature describing the clearance of iodinated MIBG in patients. After intravenous administration, MIBG shows a rapid clearance from the blood pool, with 10% or less remaining in the blood few hours after injection [28]. Clinical data have shown that I-131-MIBG is taken up quickly into the tumor cells compared to the normal tissues, with an early peak 6 h after administration [29]. The unbounded fraction of I-131-MIBG is cleared through the urine. After administration of 3.7–7.4 GBq (100–200 mCi) I-131-MIBG, the elimination half-life during the first 4 h post-infusion was 10.6 h, slightly faster in children than in adults [30]. These data is consistent with the idea that the cytotoxic effect of I-131-MIBG is due to local radioactivity rather than a general blood radioactivity.

1.2.3. Cytotoxic effect of I-131-MIBG on the neuroendocrine cells

Comparing the effect of unlabeled with radiolabeled MIBG on tumor cells, it was shown that low concentrations of MIBG are not cytotoxic. Unlabeled MIBG at 1–2 μM and up to concentrations of 10 μM has no direct effect on the cells [31,32]. Only doses $\geqslant$ 10 μM of unlabeled MIBG inhibit in a dose-dependent manner the growth of neuroblastoma cells due to a significant increase of intracellular oxidative stress [33]. As small concentrations of MIBG are used in the clinical setting due to safety measurements, the cytotoxic effect of MIBG alone is of little clinical relevance. However, when radiolabeled with I-131, even small concentrations of MIBG complex prove to be highly cytotoxic, due to a direct effect of radiation. I-131 is a beta- and gamma-emitting radionuclide with a physical half-life of 8.04 days. It owes about 90% of the cytotoxic effect on tissues to its beta radiation [34,35].

In comparison to I-131, I-123 is a iodine isotope that has a lower gamma energy and a shorter half-life of 13.13 h. This makes it not suitable for therapy but it is the considered radiopharmaceutical of choice for diagnostic imaging, necessary for MIBG therapy planning (Fig. 1).

Experimental studies showed that I-131-MIBG complex accumulates uniformly within the tumor tissue, better than the antibodies used in immunoradiotherapy which are less efficient accumulating mainly on the periphery of the tumor. The cytotoxic effect of I-131-MIBG appears relatively fast, with tumor growth significantly inhibited for up to 12 days following I-131-MIBG administration [34,35].

Comparing the cytotoxic effect of I-131-MIBG after one or repeated administration, early *in vivo* data have demonstrated that I-131-MIBG accumulation does not differ between the initial and subsequent treatments [36]. The idea that repeated administration of I-131-MIBG might be performed and have a cumulative antitumor effect persisted in the clinical setting. Clinical experience revealed that the majority of the clinical benefit with I-131-MIBG therapy occurs already after the first cycle of therapy, but further responses are frequently observed with subsequent cycles [37].

2. Therapeutic use of I-131-MIBG

2.1. Indications

Clinical experience suggests that the use of I-131-MIBG in adults with metastatic neuroendocrine tumors is advantageous

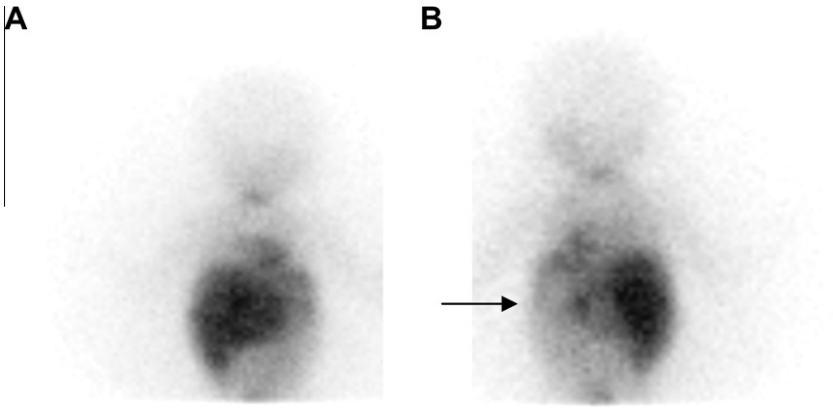

Fig. 1. Patient with hepatomegaly and with a tumoral lesions in the left adrenal gland suspected as neuroblastoma. Anterior (A) and posterior (B) view on a routine diagnostic scan obtained 24 h after the administration of 186 MBq (5 mCi) I-123-MIBG. MIBG scan shows the presence of an MIBG-positive site in the left adrenal gland. In addition, a relatively increased MIBG-uptake can be noticed diffusely in the liver. Pathologic analysis revealed the presence of neuroblastoma in the left adrenal gland and in the liver.

with respect to symptom reduction and hormone-level reduction in the majority of patients treated, and it could lead to objective anatomic responses.

As there are limited data with regard to I-131-MIBG therapy as primary therapeutic approach in patients with neuroendocrine tumors, surgery and hormonal therapy are primary therapeutic approaches [38]:

- Aggressive surgical resection of primary tumor with debulking of metastatic disease, when possible, with radiofrequency ablation and hepatic artery embolization;
- Hormonal therapy with octreotide in all symptomatic patients and those in whom there has been demonstrated increase in biochemical markers of disease, such as serum chromographin A and urinary 5-HIAA.

However, since there seems to be a survival benefit when I-131-MIBG is added to the spectrum of treatments offered to neuroendocrine tumor patients, I-131-MIBG therapy is indicated in cases of neuroendocrine tumors who are not suitable candidates for local treatment with surgery or radiofrequency ablation [6,7,38,39] or peptide receptor radiotherapy (PPRT) also discussed in this special issue. The indication includes tumors showing an adequate uptake and retention of I-131-MIBG on the basis of pre-therapy tracer study. However, biotherapy with interferon-alpha if the lesions are not MIBG-avid, can be considered as an option [38].

The following indications are stated in a current guideline for I-131-MIBG therapy [6]:

- Stage III or IV neuroblastoma;
- Inoperable pheochromocytoma;
- Inoperable paraganglioma;
- Inoperable neuroendocrine carcinomas;
- Metastatic or recurrent medullary thyroid cancer.

Based on the fact that neuroendocrine neoplasms usually express somatostatin receptors, PPRT was introduced more recently in the therapy of neuroendocrine tumors and carcinomas [40]. Neuroendocrine carcinomas, especially islet cell carcinomas, show high levels of somatostatin receptors leading to a substantial uptake of somatostatin analogs in the tumoral cells. This is in sharp contrast to the highly variable uptake of MIBG in the neuroendocrine carcinomas [41]. Moreover, it is already known that tumor dedifferentiation impacts the MIBG uptake and, thus, the efficiency of MIBG therapy. Well-differentiated malignant neuroendocrine tumors show a high MIBG uptake and high somatostatin receptor expression. In contrast, less differentiated neuroendocrine tumors or carcinomas have a much lower MIBG affinity, but preserve still the expression of somatostatin receptors [21]. These explain the better response rate of PPRT compared to the I-131-MIBG therapy.

Despite a clear decline in its use for neuroendocrine tumor therapy, I-131-MIBG remains still an alternative to PPRT. Renal insufficiency in patients with neuroendocrine tumors is an absolute contra-indication for PPRT. Due to its lack of renal toxicity, I-131-MIBG therapy is indicated in patients with inoperable metastatic neuroendocrine tumors but with renal predisposing factors.

For neuroblastoma, pheochromocytoma, paraganglioma, and medullary thyroid cancer I-131-MIBG remains still the standard radiopharmaceutical for targeted radiotherapy [42].

2.2. Contra-indications

Contra-indications for the I-131-MIBG therapy, mainly related to radiotoxicity and radiation safety, are as follows [6,42]:

- *Absolute:* pregnancy or breastfeeding, bone marrow failure and renal failure, life expectancy less than 3 months, unless in case of therapy refractory bone pain;
- *Relative:* incontinence and severe problems caused by isolation.

2.3. Preparations for therapy

Tumor stage and biologic behavior of the disease should be determined as precise as possible using imaging methods and biologic/molecular markers. I-131-MIBG scintigraphy is necessary to determine whether all lesions/clinically leading lesions have a relevant tracer uptake (Fig. 1).

2.3.1. Interactions with other medication

Medications interfering with MIBG uptake have to be withdrawn in time [6,43]. The most comprehensive overview of cardiovascular, sympathomimetic, and neurologic drugs that interfere, including advice on how long the drugs should be discontinued before I-131-MIBG can be administered can be found in a recent guideline on MIBG therapy [6].

The most commonly encountered agents that interfere with MIBG uptake and retention are alpha- and beta-adrenergic antagonists, such as pseudoephedrine and labetolol [44]. The lately is usually quite effective for treatment of neuroblastoma-associated hypertension, but must be discontinued for several days before MIBG administration. Phenothiazines may interfere with MIBG

uptake and should be avoided as sedatives before MIBG use. Serotonin re-uptake inhibitors have been listed as possibly inhibitory, but early laboratory data did not support their ability to inhibit MIBG uptake [45]. Cocaine, tricyclic antidepressants, and reserpine are very rarely encountered inhibitors of MIBG uptake, at least in children [46].

2.3.2. Thyroid blockade

Thyroid blockade is important to protect the organ from unnecessary irradiation from radioactive iodine that may dissociate from the MIBG. Thyroid blockade can be achieved using aqueous iodine solution, oral potassium iodide (100 mg adult or 2 mg/kg children) or potassium iodate commencing 2–24 h before radiopharmaceutical injection and continuing for 1 day after, in accordance with local protocols or published guidelines [6,7]. If a patient is allergic to iodine, oral potassium perchlorate may be substituted, given three times daily starting 2–24 h before and continuing for up to 5 days after, at a dose of 8 mg/kg (400 mg for adults).

2.3.3. Prevention of potential early side effects

Vomiting following the administration of the radiopharmaceutical is quite common and tends to be significantly worse in the case of large hepatic tumor burden. Ondansetron is an antiemetic of first choice.

Rarely, in adults with pheochromocytoma or paraganglioma, a significant rise in blood pressure can be observed during the administration of the radiopharamaceutical. Monitoring of the blood pressure during the infusion is, therefore, advised. Phentolamine, an alpha-adrenergic blocking agent, should be present in the administration room.

Further, a carcinoid crisis could be induced, therefore, octreotide ampules should be part of the emergency medication set, too [6].

2.3.4. Facility and personnel

As with all nuclear molecular therapies also with the usually high doses that are applied in MIBG therapies, specifically equipped rooms are necessary and only trained personal with the knowledge of radioprotection can be involved. The therapy units need to be equipped with shielded rooms, monitoring and radiation safety equipment and bathroom facilities connected to high capacity collecting tanks. The administration of I-131-MIBG should be undertaken by appropriately trained staff with supporting nursing staff and available medical physics expert [6].

2.3.5. Patient information and instructions

Careful preparations of the patients, the caretakers, and the staff have to be done before treatment to avoid unnecessary explanations during the time after I-131-MIBG infusion. Especially for small children, in whom an intensive contact might be necessary, an adequate education of the caretakers can be helpful to reduce significantly radiation exposure. The caretakers (of course no pregnant women can be allowed) should be equipped with a pocket dosimeter [42]. If necessary, a urinary catheter is placed to avoid unnecessary exposure of the patient and care providers. More than 50% of the administered dose is excreted by the urine within 48 h [30,42].

2.3.6. Administration of I-131-MIBG

I-131-MIBG should be infused over a period of at least 1 h to avoid eventual side effects of MIBG itself, mainly blood pressure changes. The substance should be administered via a central or peripheral blood catheter with a shielded infusion system to reduce radiation exposure to the staff. In neuroendocrine tumors with liver metastases intra-arterial hepatic administration achieves higher tumor doses than expected from intravenous injection, but limits the radiation to the total body [42,47,48].

During the infusion, vital signs have to be frequently monitored by the staff or an automatic blood pressure measuring system. Subsequently, enough amounts of fluid should be administered intravenously to reduce the radiation exposure of the patients by facilitating renal elimination [42].

Scintigraphy is done during the subsequent days to allow high-sensitive staging, determination of I-131-MIBG-positive tumor sites and dosimetry (Fig. 2). During the first 6 weeks blood count controls are necessary, the time intervals being dependent on the administered dose [42].

2.3.7. Potential toxicity and late side-effects of I-131-MIBG therapy

Side-effects of multiple treatments with I-131-MIBG are rather limited. Myelotoxicity is the most frequent complication of I-131-MIBG therapy. The risk of myelosuppression is more pronounced in patients who have bone marrow metastasis and when higher whole-body radiation doses are administered. However, patients have often only a transitory neutropenia which recovers within 1 week after therapy. Only a limited number of patients requires stem cell support for prolonged myelosuppression [28].

Hypothyroidism is a long-term side-effect that is quite common, despite the use of the adequate thyroid blockage with potassium iodide. The effect is mainly due to the uptake of free I-131 by the thyroid gland. Despite prophylaxis with Lugol's solution, around 25% of patients had a thyroid uptake of I-131 on the post-therapy scans following I-131-MIBG administration [49]. Most of these cases develop asymptomatic elevation of thyroid stimulating hormone. Cases of symptomatic hypothyroidism that require thyroid replacement therapy are limited, and seem to be related to higher thyroid absorbed doses [50]. However, more aggressive thyroid-blocking regimes reduce significantly the incidence of I-131 uptake in the thyroid and its subsequent dysfunction [51].

Renal toxicity is uncommon even following multiple infusions of I-131-MIBG, unlike treatments with radiolabeled somatostatin analogs.

Xerostomia is also a rare side-effect described in a few cases of parotid gland swelling after I-131-MIBG therapy, due to the known physiologic uptake of MIBG in salivary glands. However, none of them developed long-term xerostomia [52].

Secondary malignancies occur in less than 4% of patients at 5 years after I-131-MIBG therapy [53]. As malignancies occurred mostly in the area of residual neuroendocrine tumor, there is a hypothetical link between the local accumulation of I-131-MIBG, radiation, and secondary, radiation-related malignancies [54]. Isolated cases of malignancies, such as sarcoma, malignant schwanoma, or peritoneal mesothelioma, were diagnosed 1.5–14 years following I-131-MIBG therapy [55]. Possibly related to chromosomial alterations due to the effect of radiation, three of 95 patients treated with I-131-MIBG developed a myelodysplastic syndrome or acute myeloid leukemia [53].

2.3.8. Association of I-131-MIBG administration with other therapeutic modalities

Treatment with I-131-MIBG could be safely combined with external-beam radiation, since normally only a limited field is being irradiated [42].

Initial studies on combination of I-131-MIBG and chemotherapy showed limited benefit in therapy, but a significantly enhanced risk for myelotoxicity [56,57]. More recently, Mairs et al. demonstrated that the association of I-131-MIBG with topotecan, a topoisomerase I inhibitor, is effectively inducing long-term DNA damage in the tumors with only transient, minimal myelotoxicity [58]. Combining PPRT with I-131-MIBG therapy in patients with

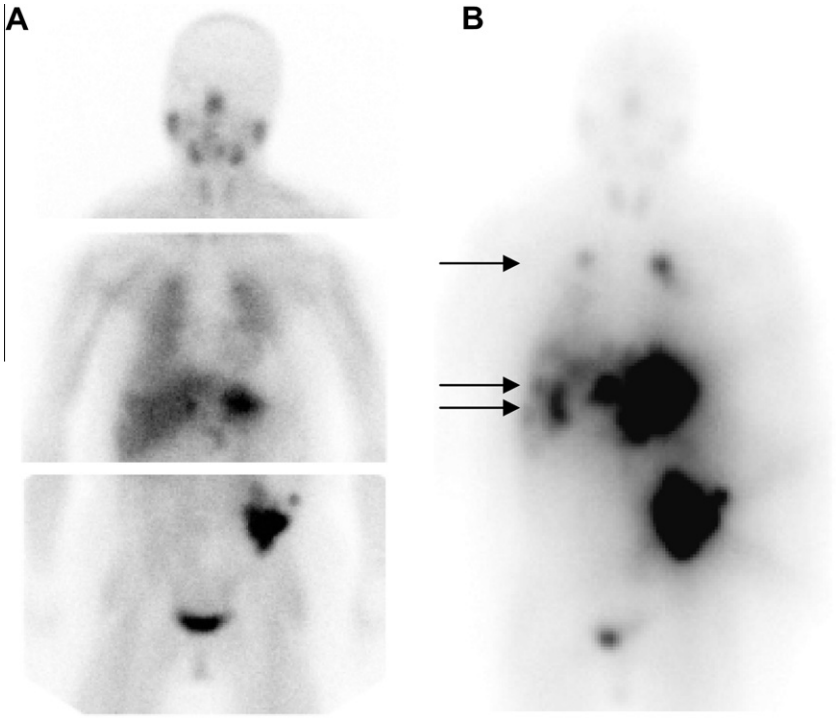

Fig. 2. Patient with neuroblastoma metastases on a routine diagnostic MIBG scan obtained 24 h after the administration of 186 MBq (5 mCi) I-123-MIBG (A). In comparison to the diagnostic scan, there is an increased detection of neuroblastoma metastases on a MIBG scan obtained 5 days following 0.5 GBq/kg I-131-MIBG administration. Arrows indicate tumor uptake seen on the post-treatment scan and not definitely seen on the diagnostic scan.

metastatic neuroendocrine tumors has already been proposed on the basis of dosimetric considerations, as the two radiopharmaceuticals do not interfere [59].

A combination of high-dose I-131-MIBG, high dose chemotherapy, autologous hematopoietic stem cell transplantation, and post-transplant immunotherapy is feasible and promising, as being associated with limited toxicity [60].

Bayer et al. demonstrated that corticosteroids can improve neuroendocrine tumor imaging and therapy. The administration of corticosteroids during I-131-MIBG therapy enhances radiopharmaceutical uptake and reduces radiation dose to non-target tissues [61].

Similarly, limited data on simultaneous use of interferon-alpha and I-131-MIBG showed no clear increase in therapy efficiency, but a significantly higher myelotoxocity than in patients treated solely with I-131-MIBG [38].

3. Clinical studies on I-131-MIBG therapy

3.1. I-131-MIBG dosimetry

Dosimetry was used to estimate tumor-specific radiation dose following I-131-MIBG therapy. Matthay et al. demonstrated that the radiation dose per tumor correlated with treatment response. They found a high probability of treatment response in those patients which had a tumor-specific radiation dose higher than 10 Gy [28].

Since I-131-MIBG is cleared through the urine, the bladder could receive a potentially limiting radiation dose. In five patients treated without bladder catheters, the mean bladder dose was 27 Gy, or aproximately 11 cGy per millicurie (11 cGy per 0.04 GBq) of I-131-MIBG administered. An unspecific I-131-MIBG uptake may occur also in other organs, such as the bone marrow [28] or in the liver and lungs [62], although to a much lower extent.

Due to higher doses used for treatment than for diagnostic purpose, post-therapy scans reveal in more than two-third of cases considerably more metastatic lesions than seen on the diagnostic scans (Fig. 2). Additional sites of disease were detected in more than two-thirds of post-treatment scans [29]. There is still no clarity whether the improved sensitivity of the post-treatment scans could impact the disease staging and patient management.

3.2. I-131-MIBG in neuroblastoma

I-131-MIBG monotherapy has been used as a molecular nuclear therapy of metastatic neuroblastoma for the last three decades. Treatment is well tolerated. Monotherapy achieves responses in 18–66% of refractory or relapsed patients, usually at doses > 0.4 GBq/kg (12 mCi/kg). For instance, lower doses of I-131-MIBG (ranging between doses of 0.1–0.5 GBq/kg (3.8–14.1 mCi/kg) [63] or total doses of 2.7–5.5 GBq (73–148 mCi) I-131-MIBG [64]), lead to an objective response rate of 31–35.7%, a few partial responses, but significant decrease in pain in the majority of patients following treatment. At somewhat higher doses of I-131-MIBG administered (mean dose of 0.38 GBq/kg, 10.3 mCi/kg), a clear increase in objective response rate has been described [65,66]. A phase I study found an objective response rate of 37% at doses of I-131-MIBG ranging from 0.1 to 0.7 GBq/kg (2.6–18 mCi/kg), with the best response in patients receiving 0.7 GBq/kg (18 mCi/kg) [67].

Repeated I-131-MIBG administration in patients with neuroblastoma was also taken in consideration. However, doses escalating I-131-MIBG therapy beyond 0.7 GBq/kg (18 mCi/kg) by administering two doses do not significantly improve the response rates [68].

The addition of high-dose chemotherapy to I-131-MIBG therapy results in an increased toxicity and no consistent improvement of the therapy [56,57]. However, treating patients with refractory neuroblastoma with a combination of I-131-MIBG and chemotherapy (cisplatin, cyclophosphamide with or without etoposide and

vincristine), a high response rate of 75% was found. The majority of patients developed a partial response, while the others showed stabilization of the disease following the combined therapy [69]. Recently, topotecan was used in combination with I-131-MIBG, with good results and minimal myelotoxicity. The best result is reached when topotecan is administered after or together with I-131-MIBG [58].

Following the I-131-MIBG success in treating relapsed neuroblastoma, recent studies were developed to evaluate the efficacy of I-131-MIBG therapy in newly diagnosed neuroblastoma. I-131-MIBG therapy shows promising results in newly diagnosed neuroblastoma patients, even before surgery. An important 66% of patients showed partial response and decrease in tumor volume after two cycles of I-131-MIBG therapy. In addition, 58% cleared their bone marrow metastases. After surgery, the response rate has already increased to a considerable 91% [70]. These results advocate for the use I-131-MIBG therapy already in the initial phase or even as a neoadjuvant approach in neuroblastoma treatment.

A current phase I study focuses on a no-carrier added form of I-131-MIBG with the potential to enhance targeting of radiation [71].

3.3. I-131-MIBG in pheocromocytoma and paraganglioma

Up to present, I-131-MIBG is the best adjunctive therapy to surgery [72]. Single or fractionated doses, as well as a variable total dosage (7.4–60 GBq, 200–1622 mCi) of I-131-MIBG have been used with response rates ranging between 30% and 47% for morphologic response and 75–90% for symptomatic response [73–76]. The reported survival rates seem encouraging especially after high-dose application [76]. Up to now, therapy with single doses of 18.5 GBq (500 mCi) showed a clear survival benefit in patients with metastatic pheochromocytoma [74]. Increased doses of I-131-MIBG beyond 18.50 GBq (500 mCi) induce a significant increase in hematological toxicity without an additional improvement in response rates compared to doses around or less than 18.5 GBq (500 mCi) [76–78]. Therefore, doses of 15.0–18.5 GBq (405–500 mCi) are proposed as the routine initial dose in treatment of pheochromocytoma and paragangliomas.

In case of metastatic foci, I-131-MIBG produces a better response compared to palliative chemotherapy [79]. Out of the 60% of the metastatic foci which showed avid uptake of I-131-MIBG, approximately 30% demonstrated objective response to therapy [78]. In about 40% of the cases, tumors remain stable after I-131-MIBG therapy [72].

Potentially new molecular targeting approaches such as multikinase inhibitors [80] and PRRT [81] were proposed. However, I-131-MIBG remains the best adjunctive therapy to surgery for targeted radiotherapy of chromaffin tumors. The newer PPRT is only considered a reserve treatment option in case of tumor cell de-differentiation with associated decrease or loss of MIBG uptake [42].

3.4. I-131-MIBG therapy in medullary thyroid carcinoma

The therapeutic use of I-131-MIBG in medullary thyroid carcinoma was tested only in a limited number of patients, due in part to the rare incidence of the tumor and the variable ability of lesions to take up the tracer [82]. Therefore, the indication of I-131-MIBG therapy in medullary thyroid carcinoma is mainly for palliation of inoperable metastatic disease. MIBG uptake, which is encountered in about one-third of patients with this tumor entity, is an absolute requisite for a successful treatment. Treatment protocol is similar to that applied for malignant pheochromocytoma and includes doses of 7.4–11.1 GBq (200–300 mCi) I-131-MIBG infusion over a period of 45–60 min. Therapy is repeated at 3–6 months interval [43]. The objective response rate of I-131-MIBG therapy in metastatic medullary thyroid carcinoma is around 30%, while another half of the patients may be stabilized [83]. Patients will benefit most from symptomatic improvement in the presence of functioning disease. At least 50% of these patients will experience significant decrease in hormone-related symptoms, which can be of dramatic effect for life quality [43].

In case of a low intensity of MIBG uptake demonstrated on pretherapy scans, I-131-MIBG therapy is considered to be ineffective. However, clinical experience of I-131-MIBG therapy performed as ultima ratio in a few patients which were unresponsive to any other established therapy regimens, showed a surprising stabilization of the disease, at least for a duration of 12–20 months [83]. Therefore, a more extensive role of I-131-MIBG therapy in medullary thyroid carcinoma should be addressed.

3.5. I-131-MIBG therapy in neuroendocrine carcinomas

Accumulating evidence in the literature indicates a positive role of I-131-MIBG therapy for neuroendocrine carcinomas. If taken up by the tumor lesions, I-131-MIBG therapy induces a significant, long-lasting reduction of tumor-related symptoms, with reported rates of symptomatic response in the range of 50–75% [84,85]. The pronounced symptomatic effect of I-131-MIBG treatment often occurs without adequate biochemical response, such as decrease of urinary hydroxyindolacetic acid or serum chromogranin A. This discrepancy is not fully understood, being probably linked to unknown hormonal factors that may account for symptomatic carcinoid disease [86]. The observed trend to prolonged survival after application of higher initial activities makes dose-intensified concepts using >11.1 GBq (>300 mCi) favorable [87].

Due to the success of the newer PPRT treatment in neuroendocrine carcinomas, the interest in I-131-MIBG therapy has substantially decreased. Considering still the capacity of I-131-MIBG therapy in arresting tumor progression and prolonging survival, a combination PPRT with I-131-MIBG therapy has been suggested on the basis of dosimetric considerations [59].

One limitation of PPRT is the risk of renal insufficiency induction, making it impossible to be performed in patients presenting already with a clinically compensated but relevant impaired renal function (i.e. creatinine clearance below 50 ml/min). As MIBG is lacking significant renal irradiation, and thus toxicity, it makes it a good alternative for treatment of neuroendocrine carcinoma patients with kidney disease [42].

3.6. I-131-MIBG therapy in other tumors

The use of I-131-MIBG in other rare, sporadic neuroendocrine tumors, such as islet cell carcinoma and Merkel cell carcinoma, has become completely dispensable due to the emergence of PPRT [42]. Initial experience has been reported from studies on mixed tumor cohorts including successful treatment in sporadic patients of these tumor types [42,88].

4. No-carrier-added I-131-MIBG, a novel concept in I-131-MIBG therapy

The standard I-131-MIBG used for treatment is produced by exchange of radioiodine for stable iodine in the I-127-MIBG molecule [58]. There is an excessive amount of "cold" MIBG in the yielded radiopharmaceutical associated with this relatively ineffective method – only 1 of 2000 molecules will be the radioactive compound [89]. Currently, no-carrier-added (high-specific-activity) I-131-MIBG (AzedraTM; Molecular Insight Pharmaceuticals,

Cambridge, MA) is being investigated. The producer's hypothesis is that unlabeled MIBG does not provide therapeutic benefits and that it may provide unwanted side-effects and compete with therapeutic I-131-MIBG for binding on target-receptors sites, thereby potentially affecting efficacy [90]. The high-specific activity I-131-MIBG, yielded by a different method of synthesis [89], may constitute a significant improvement in this regard. High-specific-activity I-131-MIBG has been used in a phase I dose-finding study [90]. Currently, a phase II study is being conducted. Patients will receive two doses of 18.5 GBq (500 mCi) or 0.3 GBq/kg (8 mCi/kg) of high-specific activity I-131-MIBG 3 months apart (ClinicalTrials.gov 2009).

5. Conclusions

Despite a high variability in doses used, therapeutic combinations, and outcome, reasonable amount of studies have demonstrated that I-131-MIBG therapy is an effective and safe treatment modality for neuroendocrine tumors. I-131-MIBG remains the most used therapeutic modality for metastatic pheochromocytoma and paraganglioma. Used mainly in late stage of neuroblastoma, its beneficial effect in treatment of early stages of neuroblastoma is being considered. Despite development of new agents for treatment, such as PPRT, I-131-MIBG therapy remains a valuable therapeutic alternative. Clinical studies on potential improvement of the therapeutic effect of I-131-MIBG are recently under investigation.

References

[1] D.M. Wieland, J. Wu, L.E. Brown, T.J. Mangner, D.P. Swanson, W.H. Beierwaltes, J. Nucl. Med. 21 (1980) 349–353.
[2] A.J. McEwan, B. Shapiro, J.C. Sisson, W.H. Beierwaltes, D.M. Ackery, Semin. Nucl. Med. 15 (1985) 132–153.
[3] J.C. Sisson, B. Shapiro, W.H. Beierwaltes, Henry Ford Hosp. Med. J. 32 (1984) 254–261.
[4] J. Treuner, T. Klingebiel, U. Feine, J. Buck, G. Bruchelt, R. Dopfer, R. Girgert, W. Muller-Schauenburg, J. Meinke, W. Kaiser, et al., Pediatr. Hematol. Oncol. 3 (1986) 205–216.
[5] C.A. Hoefnagel, F.C. den Hartog Jager, A.H. van Gennip, H.R. Marcuse, B.G. Taal, Clin. Nucl. Med. 11 (1986) 150–152.
[6] F. Giammarile, A. Chiti, M. Lassmann, B. Brans, G. Flux, Eur. J. Nucl. Med. Mol. Imaging 35 (2008) 1039–1047.
[7] P. Olivier, P. Colarinha, J. Fettich, S. Fischer, J. Frokier, F. Giammarile, I. Gordon, K. Hahn, L. Kabasakal, M. Mann, M. Mitjavila, A. Piepsz, U. Porn, R. Sixt, J. van Velzen, Eur. J. Nucl. Med. Mol. Imaging 30 (2003) 45–50.
[8] K.K. Matthay, J.G. Villablanca, R.C. Seeger, D.O. Stram, R.E. Harris, N.K. Ramsay, P. Swift, H. Shimada, C.T. Black, G.M. Brodeur, R.B. Gerbing, C.P. Reynolds, N. Engl. J. Med. 341 (1999) 1165–1173.
[9] F. Berthold, J. Boos, S. Burdach, R. Erttmann, G. Henze, J. Hermann, T. Klingebiel, B. Kremens, F.H. Schilling, M. Schrappe, T. Simon, B. Hero, Lancet Oncol. 6 (2005) 649–658.
[10] J.M. Maris, N. Engl. J. Med. 362 (2010) 2202–2211.
[11] A.E. Evans, G.J. D'Angio, J. Clin. Oncol. 23 (2005) 6443–6444.
[12] R. Howman-Giles, P.J. Shaw, R.F. Uren, D.K. Chung, Semin. Nucl. Med. 37 (2007) 286–302.
[13] R.E. George, W.B. London, S.L. Cohn, J.M. Maris, C. Kretschmar, L. Diller, G.M. Brodeur, R.P. Castleberry, A.T. Look, J. Clin. Oncol. 23 (2005) 6466–6473.
[14] R. Ladenstein, T. Philip, C. Lasset, O. Hartmann, A. Garaventa, R. Pinkerton, J. Michon, J. Pritchard, T. Klingebiel, B. Kremens, A. Pearson, C. Coze, P. Paolucci, D. Frappaz, H. Gadner, F. Chauvin, J. Clin. Oncol. 16 (1998) 953–965.
[15] A. Iavarone, A. Lasorella, T. Servidei, R. Riccardi, L. Troncone, R. Mastrangelo, J. Nucl. Biol. Med. 35 (1991) 186–190.
[16] A. Iavarone, A. Lasorella, T. Servidei, R. Riccardi, R. Mastrangelo, Cancer Res. 53 (1993) 304–309.
[17] S. Carlin, R.J. Mairs, A.G. McCluskey, D.A. Tweddle, A. Sprigg, C. Estlin, J. Board, R.E. George, C. Ellershaw, A.D. Pearson, J. Lunec, P.G. Montaldo, M. Ponzoni, B.L. van Eck-Smit, C.A. Hoefnagel, M.D. van den Brug, G.A. Tytgat, H.N. Caron, Clin. Cancer Res. 9 (2003) 3338–3344.
[18] A. Altmann, M. Kissel, S. Zitzmann, W. Kubler, M. Mahmut, P. Peschke, U. Haberkorn, J. Nucl. Med. 44 (2003) 973–980.
[19] L.S. Lashford, J.P. Hancock, J.T. Kemshead, Int. J. Cancer 47 (1991) 105–109.
[20] M.N. Gaze, I.M. Huxham, R.J. Mairs, A. Barrett, Int. J. Cancer 47 (1991) 875–880.
[21] S. Ezziddin, T. Logvinski, C. Yong-Hing, H. Ahmadzadehfar, H.P. Fischer, H. Palmedo, J. Bucerius, M.J. Reinhardt, H.J. Biersack, J. Nucl. Med. (2006) 223–233.
[22] P.G. Montaldo, L. Raffaghello, F. Guarnaccia, V. Pistoia, A. Garaventa, M. Ponzoni, Int. J. Cancer 67 (1996) 95–100.
[23] B. Luzon-Toro, A. Geerlings, S. Hilfiker, Nucl. Med. Biol. 35 (2008) 801–804.
[24] A. Armour, S.H. Cunningham, M.N. Gaze, T.E. Wheldon, R.J. Mairs, Br. J. Cancer 75 (1997) 470–476.
[25] D. Meco, A. Lasorella, A. Riccardi, T. Servidei, R. Mastrangelo, R. Riccardi, Eur. J. Cancer 35 (1999) 1227–1234.
[26] A.G. McCluskey, M. Boyd, S.C. Ross, E. Cosimo, A.M. Clark, W.J. Angerson, M.N. Gaze, R.J. Mairs, Clin. Cancer Res. 11 (2005) 7929–7937.
[27] A.G. McCluskey, M. Boyd, M.N. Gaze, R.J. Mairs, Cancer Lett. 228 (2005) 221–227.
[28] K.K. Matthay, C. Panina, J. Huberty, D. Price, D.V. Glidden, H.R. Tang, R.A. Hawkins, J. Veatch, B. Hasegawa, J. Nucl. Med. 42 (2001) 1713–1721.
[29] M.P. Hickeson, M. Charron, J.M. Maris, P. Brophy, T.I. Kang, H. Zhuang, J. Khan, T. Nevrotski, Pediatr. Blood Cancer 42 (2004) 268–274.
[30] A.R. Wafelman, Y.L. Nortier, H. Rosing, H.J. Maessen, B.G. Taal, C.A. Hoefnagel, R.A. Maes, J.H. Beijnen, Nucl. Med. Commun. 16 (1995) 767–772.
[31] M.N. Gaze, R.J. Mairs, S.M. Boyack, T.E. Wheldon, A. Barrett, Br. J. Cancer 66 (1992) 1048–1052.
[32] G. Bruchelt, R. Girgert, J. Buck, H. Wolburg, D. Niethammer, J. Treuner, Cancer Res. 48 (1988) 2993–2997.
[33] J. Cornelissen, A.B. van Kuilenburg, P.A. Voute, A.H. van Gennip, Int. J. Cancer 72 (1997) 486–490.
[34] M. Rutgers, C.K. Buitenhuis, M.A. van der Valk, C.A. Hoefnagel, P.A. Voute, L.A. Smets, Int. J. Cancer 90 (2000) 312–325.
[35] R.J. Mairs, W. Angerson, M.N. Gaze, T. Murray, J.W. Babich, R. Reid, C. McSharry, Br. J. Cancer 63 (1991) 404–409.
[36] M. Rutgers, C.K. Buitenhuis, C.A. Hoefnagel, P.A. Voute, L.A. Smets, Int. J. Cancer 87 (2000) 412–422.
[37] J.P. Howard, J.M. Maris, L.S. Kersun, J.P. Huberty, S.C. Cheng, R.A. Hawkins, K.K. Matthay, Pediatr. Blood Cancer 44 (2005) 232–239.
[38] E.J. Postema, A.J. McEwan, Cancer Biother. Radiopharm. 24 (2009) 519–525.
[39] M.S. Sywak, J.L. Pasieka, A. McEwan, G. Kline, O. Rorstad, World J. Surg. 28 (2004) 1157–1162.
[40] A. Sowa-Staszczak, D. Pach, R. Chrzan, M. Trofimiuk, A. Stefanska, M. Tomaszuk, M. Kolodziej, R. Mikolajczak, D. Pawlak, A. Hubalewska-Dydejczyk, Eur. J. Nucl. Med. Mol. Imaging (2011).
[41] D.J. Kwekkeboom, W.W. de Herder, B.L. Kam, C.H. van Eijck, M. van Essen, P.P. Kooij, R.A. Feelders, M.O. van Aken, E.P. Krenning, J. Clin. Oncol. 26 (2008) 2124–2130.
[42] F. Grunwald, S. Ezziddin, Semin. Nucl. Med. 40 (2010) 153–163.
[43] K. Zaplatnikov, C. Menzel, N. Dobert, N. Hamscho, W.T. Kranert, M. Gotthard, T.M. Behr, F. Grunwald, Br. J. Radiol. 77 (2004) 525–527.
[44] J.W. Babich, W. Graham, A.J. Fischman, Eur. J. Nucl. Med. 24 (1997) 538–543.
[45] D. Guilloteau, S. Chalon, J.L. Baulieu, F. Huguet, G. Desplanches, C. Chambon, M.P. Vilar, L. Pourcelot, J.C. Besnard, Eur. J. Nucl. Med. 14 (1988) 341–344.
[46] K.K. Matthay, B. Shulkin, R. Ladenstein, J. Michon, F. Giammarile, V. Lewington, A.D. Pearson, S.L. Cohn, Br. J. Cancer 102 (2010) 1319–1326.
[47] C. Brogsitter, J. Pinkert, J. Bredow, T. Kittner, J. Kotzerke, J. Nucl. Med. 46 (2005) 2112–2116.
[48] M. Popp, A. Strumpf, K. Zöphel, C. Stroszczynski, J. Kotzerke, Eur. J. Nucl. Med. 37 (2010) 180.
[49] H.M. van Santen, J. de Kraker, T. Vulsma, Eur. J. Cancer 41 (2005) 1767–1774.
[50] B. Brans, M. Monsieurs, G. Laureys, J.M. Kaufman, H. Thierens, R.A. Dierckx, Med. Pediatr. Oncol. 38 (2002) 41–46.
[51] A. Quach, L. Ji, V. Mishra, A. Sznewajs, J. Veatch, J. Huberty, B. Franc, R. Sposto, S. Groshen, D. Wei, P. Fitzgerald, J.M. Maris, G. Yanik, R.A. Hawkins, J.G. Villablanca, K.K. Matthay, Pediatr. Blood Cancer 56 (2011) 191–201.
[52] S. Modak, N. Pandit-Taskar, B.H. Kushner, K. Kramer, P. Smith-Jones, S. Larson, N.K. Cheung, Pediatr. Blood Cancer 50 (2008) 1271–1273.
[53] B. Weiss, A. Vora, J. Huberty, R.A. Hawkins, K.K. Matthay, J. Pediatr. Hematol. Oncol. 25 (2003) 543–547.
[54] K.K. Matthay, G. Yanik, J. Messina, A. Quach, J. Huberty, S.C. Cheng, J. Veatch, R. Goldsby, P. Brophy, L.S. Kersun, R.A. Hawkins, J.M. Maris, J. Clin. Oncol. 25 (2007) 1054–1060.
[55] A. Garaventa, C. Gambini, G. Villavecchia, A. Di Cataldo, L. Bertolazzi, M.R. Pizzitola, B. De Bernardi, R. Haupt, Cancer 97 (2003) 1332–1338.
[56] G.A. Yanik, J.E. Levine, K.K. Matthay, J.C. Sisson, B.L. Shulkin, B. Shapiro, D. Hubers, S. Spalding, T. Braun, J.L. Ferrara, R.J. Hutchinson, J. Clin. Oncol. 20 (2002) 2142–2149.
[57] M. Schmidt, T. Simon, B. Hero, W. Eschner, M. Dietlein, F. Sudbrock, R. Bongartz, F. Berthold, H. Schicha, Nuklearmedizin 45 (2006). 145-145.
[58] R.J. Mairs, M. Boyd, Nucl. Med. Biol. 35 (2008) 9–20.
[59] M.T. Madsen, D.L. Bushnell, M.E. Juweid, Y. Menda, M.S. O'Dorisio, T. O'Dorisio, I.M. Besse, J. Nucl. Med. 47 (2006) 660–667.
[60] J. Toporski, M. Garkavij, J. Tennvall, I. Ora, K.S. Gleisner, J.H. Dykes, S. Lenhoff, G. Juliusson, S. Scheding, D. Turkiewicz, A.N. Bekassy, Biol. Blood Marrow Transplant. 15 (2009) 1077–1085.
[61] M. Bayer, Z. Kuci, E. Schomig, D. Grundemann, H. Dittmann, R. Handgretinger, G. Bruchelt, Nucl. Med. Biol. 36 (2009) 287–294.
[62] A.A. Bolster, T.E. Hilditch, T.E. Wheldon, M.N. Gaze, A. Barrett, Br. J. Radiol. 68 (1995) 481–490.
[63] T.I. Kang, P. Brophy, M. Hickeson, S. Heyman, A.E. Evans, M. Charron, J.M. Maris, J. Pediatr. Hematol. Oncol. 25 (2003) 769–773.
[64] M.R. Castellani, A. Chiti, E. Seregni, E. Bombardieri, Q. J. Nucl. Med. 44 (2000) 77–87.

[65] T. Klingebiel, F. Berthold, J. Treuner, D. Schwabe, M. Fischer, U. Feine, F.D. Maul, W. Waters, H. Wehinger, D. Niethammer, Med. Pediatr. Oncol. 19 (1991) 84–88.
[66] T. Klingebiel, U. Feine, J. Treuner, P. Reuland, R. Handgretinger, D. Niethammer, J. Nucl. Biol. Med. 35 (1991) 216–219.
[67] K.K. Matthay, K. DeSantes, B. Hasegawa, J. Huberty, R.S. Hattner, A. Ablin, C.P. Reynolds, R.C. Seeger, V.K. Weinberg, D. Price, J. Clin. Oncol. 16 (1998) 229–236.
[68] K.K. Matthay, A. Quach, J. Huberty, B.L. Franc, R.A. Hawkins, H. Jackson, S. Groshen, S. Shusterman, G. Yanik, J. Veatch, P. Brophy, J.G. Villablanca, J.M. Maris, J. Clin. Oncol. 27 (2009) 1020–1025.
[69] S. Mastrangelo, A. Tornesello, L. Diociaiuti, A. Pession, A. Prete, V. Rufini, L. Troncone, R. Mastrangelo, Br. J. Cancer 84 (2001) 460–464.
[70] J. de Kraker, K.A. Hoefnagel, A.C. Verschuur, B. van Eck, H.M. van Santen, H.N. Caron, Eur. J. Cancer 44 (2008) 551–556.
[71] S. Modak, N.K. Cheung, Cancer Treat. Rev. 36 (2010) 307–317.
[72] A. Chrisoulidou, G. Kaltsas, I. Ilias, A.B. Grossman, Endocr. Relat. Cancer 14 (2007) 569–585.
[73] G.A. Kaltsas, D. Papadogias, P. Makras, A.B. Grossman, Endocr. Relat. Cancer 12 (2005) 683–699.
[74] S.D. Safford, R.E. Coleman, J.P. Gockerman, J. Moore, J. Feldman, M.W. Onaitis, D.S. Tyler, J.A. Olson Jr., Cancer 101 (2004) 1987–1993.
[75] G.K. Gedik, C.A. Hoefnagel, E. Bais, R.A. Olmos, Eur. J. Nucl. Med. Mol. Imaging 35 (2008) 725–733.
[76] S. Gonias, R. Goldsby, K.K. Matthay, R. Hawkins, D. Price, J. Huberty, L. Damon, C. Linker, A. Sznewajs, S. Shiboski, P. Fitzgerald, J. Clin. Oncol. 27 (2009) 4162–4168.
[77] B. Rose, K.K. Matthay, D. Price, J. Huberty, B. Klencke, J.A. Norton, P.A. Fitzgerald, Cancer 98 (2003) 239–248.
[78] P.A. Fitzgerald, R.E. Goldsby, J.P. Huberty, D.C. Price, R.A. Hawkins, J.J. Veatch, F. Dela Cruz, T.M. Jahan, C.A. Linker, L. Damon, K.K. Matthay, Ann. N. Y. Acad. Sci. 1073 (2006) 465–490.
[79] A. Szalat, M. Fraenkel, V. Doviner, A. Salmon, D.J. Gross, Endocr. 39 (2011) 160–166.
[80] M. Fassnacht, M.C. Kreissl, D. Weismann, B. Allolio, Pharmacol. Ther. 123 (2009) 117–141.
[81] F. Forrer, I. Riedweg, H.R. Maecke, J. Mueller-Brand, Q. J. Nucl. Med. Mol. Imaging 52 (2008) 334–340.
[82] M.R. Castellani, A. Alessi, G. Savelli, E. Bombardieri, Tumori 89 (2003) 560–562.
[83] M.R. Castellani, E. Seregni, M. Maccauro, C. Chiesa, G. Aliberti, E. Orunesu, E. Bombardieri, Q. J. Nucl. Med. Mol. Imaging 52 (2008) 430–440.
[84] J.R. Buscombe, J.B. Cwikla, M.E. Caplin, A.J. Hilson, Nucl. Med. Commun. 26 (2005) 969–976.
[85] A.C. Nwosu, L. Jones, J. Vora, G.J. Poston, S. Vinjamuri, D.M. Pritchard, Br. J. Cancer 98 (2008) 1053–1058.
[86] J.L. Pasieka, A.J. McEwan, O. Rorstad, Surgery 136 (2004) 1218–1226.
[87] S.D. Safford, R.E. Coleman, J.P. Gockerman, J. Moore, J.M. Feldman, G.S. Leight Jr., D.S. Tyler, J.A. Olson Jr., Surgery 134 (2003) 956–962.
[88] C.A. Hoefnagel, Eur. J. Nucl. Med. 21 (1994) 561–581.
[89] G. Vaidyanathan, M.R. Zalutsky, Appl. Radiat. Isot. 44 (1993) 621–628.
[90] R.E. Coleman, J.B. Stubbs, J.A. Barrett, M. de la Guardia, N. Lafrance, J.W. Babich, Cancer Biother. Radiopharm. 24 (2009) 469–475.