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131-I MIBG therapy of malignant pheochromocytoma and paraganglioma tumours — a single-centre study

Terapia radioizotopowa 131-MIBG złośliwych guzów chromochłonnych i przyzwojaków — badanie jednoośrodkowe

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Abstract

Introduction: Pheochromocytomas and paragangliomas are rare tumours deriving from chromaffin cells of adrenal medulla or paraganglia. They are usually benign, but 10–35% of them present malignant behaviour. The aim of the study was to evaluate the efficacy and safety of 131-I MIBG therapy in malignant pheochromocytoma /paraganglioma patients (MPPGL).

Material and methods: Eighteen patients (7 women and 11 men) were included in this study. Between 2002 and 2016 they underwent 131-I MIBG therapy because of MPPGL, and their medical data were analysed retrospectively. Clinical indications for the treatment included progressive disease or massive tissue involvement independently of disease progression. Tumour response for the first time was assessed three months after the last treatment, according to *Response Evaluation Criteria in Solid Tumours* criteria and by 131-I MIBG scans.

Results: The mean single dose used was 7.25 GBq (196 mCi) and mean cumulative dose 33.08 GBq (894 mCi). In two (11%) patients complete tumour response was achieved. In one (6%) patient partial response was obtained. In 13 (72%) patients stable disease was observed. In two (11%) patients progression was diagnosed three months after treatment discontinuation. In the whole studied group the progression-free survival time was 85 months and overall five-year survival was 87%.

Conclusions: Radionuclide treatment with use of 131-I MIBG may be an effective form of palliative treatment for patients with inoperative neoplasm spread or progressive disease, or patients requiring alleviation of symptoms. **(Endokrynol Pol 2018; 69 (3): 246–251)**

Key words: *pheochromocytoma, paraganglioma, MIBG treatment*

Streszczenie

Wstęp: Guzy chromochłonne i przyzwojaki są rzadkimi guzami wywodzącymi się z tkanki chromochłonnej rdzenia nadnerczy i ciałek przyzwojowych. Zwykle są to nowotwory łagodne, jednak w 10–35% mogą prezentować potencjał złośliwy. Celem pracy była ocena skuteczności i bezpieczeństwa leczenia radioizotopowego 131-I MIBG w złośliwych guzach chromochłonnych i przyzwojakach poddawanych terapii w pojedynczym ośrodku onkologicznym.

Materiał i metody: Do badania włączono 18 pacjentów (7 kobiet, 11 mężczyzn). Dokumentacja medyczna pacjentów ze złośliwymi guzami chromochłonnymi i przyzwojakami, którzy zostali poddani leczeniu radioizotopowemu 131-I MIBG w latach 2002–2016 została przeanalizowana retrospektywnie. Kliniczne wskazania do terapii obejmowały progresję choroby (5 pacjentów), dużą masę nowotworu niezależnie od dynamiki choroby (13 pacjentów). Odpowiedź na leczenie oceniano po raz pierwszy po 3 miesiącach przy użyciu tomografii komputerowej według kryteriów *Response Evaluation Criteria in Solid Tumors* oraz scyntygrafii 131-MIBG .

Wyniki: Średnia pojedyncza dawka radiofarmaceutyku zastosowana podczas leczenia wynosiła 7,25 GBq (196 mCi), średnia skumulowana 33,08 GBq (894 mCi). Średni czas obserwacji pacjentów po leczeniu wynosił 78 miesięcy (zakres: 7–197 mies.). U 2 pacjentów (11%) uzyskano całkowitą remisję, u 1 pacjenta (6%) częściową remisję, a u 13 pacjentów (72%) obserwowano stabilną chorobę. U 2 pacjentów (11%) 3 miesiące po zakończeniu leczenia potwierdzono progresję choroby. W całej analizowanej grupie czas wolny do progresji wyniósł 85 miesięcy, a 5-letnie przeżycie 87%.

Wnioski: Leczenie radioizotopowe z użyciem 131-I MIBG może być efektywną metodą leczenia paliatywnego złośliwych guzów chromochłonnych lub przyzwojaków w przypadku choroby nieoperacyjnej, rozsianej, z potwierdzoną progresją, czy też u pacjentów wymagających leczenia objawowego. **(Endokrynol Pol 2018; 69 (3): 246–251)**

Słowa kluczowe: *guz chromochłonny, przyzwojak, leczenie radioizotopowe 131-I MIBG*

Introduction

Pheochromocytomas and paragangliomas are rare tumours deriving from chromaffin cells of adrenal medulla or paraganglia, able to synthesise, store, and secrete catecholamines or their metabolites. They are usually benign, but 10–35% of them present malignant behaviour [1, 2]. Several biochemical, morphologi-

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cal, and molecular markers of malignancy have been investigated, but the only reliable criterion generally agreed is the presence of distant metastases in non-chromaffin tissues [3]. Complete surgical excision of the tumour is the treatment of choice. In the presence of neoplasm spread palliative treatment is the only option [4]. Among them, 131-I MIBG therapy, introduced into the treatment in 1984, is the most widely used. Metaiodobenzylguanidine (MIBG) is a substrate for transmembrane noradrenaline transporter (NAT) actively captured and stored in presynaptic sympathetic nerve terminals (and also in tumour cells). Its coupling with 131-I enables tumour cell damage by the action of beta particles [5, 6]. About 60% of metastatic foci show avid uptake of 131-I MIBG, and approximately 30% of them demonstrate objective response to the therapy [4, 7]. An additional 40% of the tumours remain stable [6, 8]. There are no strict recommendations about the doses and schedules used because only a few studies, with small patient groups, have been published.

The aim of the study was to evaluate the efficacy and safety of 131-I MIBG therapy in malignant pheochromocytoma/paraganglioma patients treated in a single endocrine oncology centre.

Material and methods

Eighteen patients (7 women and 11 men) were included in this study. Between 2002 and 2016 they underwent 131-I MIBG therapy because of malignant pheochromocytoma or paraganglioma tumours (MPPGL), and their medical data were analysed retrospectively. In 10 (55%) patients pheochromocytoma was diagnosed, and in eight (45%) cases paraganglioma. In 15 (83%) patients the diagnosis was confirmed in histological examination after primary tumour resection, and in the remaining three (17%) in histological analysis of specimens obtained on core-needle biopsy or explorative laparotomy. The presence of metastases was confirmed by radiologic modalities (CT or MRI) and radionuclide imaging (^{131}I or ^{123}I MIBG scans). Hormonal activity of the tumour was assessed by measuring total or fractionated metanephrines in 24-h urinary excretion. The results of 24-h urinary excretion measurements were available for 14 patients. Clinical characteristics of whole group are shown in Table I. Genotyping of the main PPGL susceptibility genes (RET, VHL, SDHB, SDHD, MAX, and TMEM 127) was performed in each patient. The genetic status of the group is illustrated in Table II.

Once the extent of disease was evaluated, therapy options were discussed on the multidisciplinary board team meetings. Patients without the possibility of using loco regional procedures and with avid MIBG uptake on diagnostic imaging were qualified for radionuclide treatment with the use of ^{131}I-MIBG. Clinical indications for the treatment included progressive disease (five patients) or massive tissue involvement independently of disease progression (13 patients).

Complete clinical evaluation, blood count, and serum chemistry analyses were conducted before the therapy procedure.

Table I. *Clinical characteristics of the cohort*

Tabela I. *Charakterystyka kliniczna analizowanej grupy*

Diagnosis	No of patients (%)
pheochromocytoma	10 (56%)
paraganglioma	8 (45%)
Gender	No. of patients (%)
female	7 (39%)
male	11 (61%)
Hormonal activity of the tumour	No of patients (%)
present	8/14 (57%)
absent	6/14 (43%)
Localisation of metastases	No. of patients (%)
soft tissues (lymph nodes, lung, liver)	8 (44%)
bones exclusively or with soft tissues	10 (56%)
Time from diagnosis to metastases occurrence	Years
mean	5.2
range	0-20
Age at the time of treatment	Years
mean	43.6
range	11-84
Prior treatment	No of patients (%)
resection of primary lesion	15 (83%)
loco regional surgery (metastases or local recurrence removal)	3 (17%)
chemotherapy	2 (11%)
radiotherapy	1 (6%)

Table II. *Genetic status of patients with MPPGL treated with use of 131-MIBG*

Tabela II. *Wyniki analizy DNA u pacjentów ze złośliwymi guzami chromochłonnymi i przyzwojakami leczonych radioizotopowow przy użyciu MIBG 131-I*

Genetic status	**No. of patients (%)**
SDHB	3 (17%)
RET	1 (6 %)
VHL	1 (6%)
NF1	1 (6%)
No mutation found	11 (65%)

Sodium perchlorate or potassium iodide were used for thyroid protection.

A standard 131-I MIBG protocol included five courses of 7.4 GBq (200 mCi) activity repeated in 12-week intervals. In some patients, individual adjustments were made. 131-I MIBG was administered intravenously over a two-hour period. Patients were isolated until the radiation dose rate measured at 1 m decreased to less than 20 uSv/h. At that time post-therapy whole body scintigraphy was performed.

Tumour response for the first time was assessed after the last treatment by CT according to *Response Evaluation Criteria in Solid Tumours (RECIST)* criteria and by 131-I MIBG scans evaluated on the basis of the interpretation of an assessing nuclear medicine specialist. Urinary metanephrines were measured only in patients with elevated values prior to treatment. At least 50% decrease in diurnal excretion was defined as post-therapeutic hormonal response.

Adverse events were evaluated according to *Common Terminology Criteria for Adverse Events 3.0.*

Clinical, biochemical, and radiological status was under surveillance annually. If needed, radionuclide imaging was performed.

Overall survival was determined by using the Kaplan-Meyer method.

Results

The mean single dose used was 7.25 GBq (196 mCi) and mean cumulative dose 33.08 GBq (894 mCi). Mean time of follow-up after treatment was 78 months (range 7–197 months).

Complete response was obtained in two patients with lymph node and bone metastases. There was no disease relapse during follow-up (respectively, 100 and 197 months).

Partial response was observed in one patient, who remained stable for 60 months. Subsequently, because of progression, peptide receptor radionuclide therapy (PRRT) was performed.

In 13 (72%) patients stable disease was the best response to 131-I MIBG therapy. Among the group of 13 patients with stable disease assessed three months after the last treatment course, four patients were progressive prior to treatment. In the remaining nine patients progression was not confirmed prior to 131-MIBG therapy. In the group of patients progressive prior to treatment three remained stable in the follow-up period (14–150 months), in one we observed extension of the disease after 85 months. In the cohort of patients with stabilisation of disease after 131-I MIBG therapy and without progression prior the treatment eight remained stable in follow-up (4–127 months) and one progressed after 34 months.

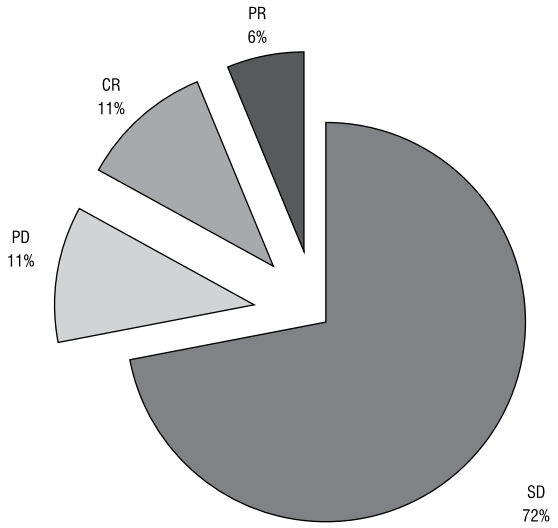

Figure 1. *Early results of the 131-I MIBG treatment (evaluated 3 months after the last treatment course)*

CR — *complete response, PR — partial response, SD — stable disease, PD — progressive disease*

Rycina 1. *Wczesne efekty leczenia radioizotopowego przy użyciu 131-I MIBG (oceniane 3 miesiące po podaniu ostatniej aktywności)*

CR — *całkowita remisja, PR — częściowa remisja, SD — stabilna choroba, PD — progresja*

Progressive disease three months after treatment discontinuation was observed in two patients: SDHB mutation male carrier with lymph node metastases (progressive also prior treatment); and sporadic pheochromocytoma in a male patient with metastases localised in bones and soft tissues.

Results of the 131-I MIBG treatment are illustrated in Figure 1.

Although all patients underwent analysis of genetic status, a relatively small number of patients with mutation (Tab. I) enabled statistical analysis of differences in response to the 131-I MIBG treatment. The most common mutation found was SDHB. The characteristic of this group and efficacy of treatment is summarised in Table III.

In the whole studied group, the progression-free survival time was 85 months and five-year survival was 87%. The Kaplan-Meyer survival curve is illustrated in Figure 2.

Hormonal response to the radionuclide therapy was obtained in all eight patients with hormonal activity confirmed before treatment. Normalisation of metanephrines excretion was seen in four (50%) of them. In seven patients hormonal response was accompanied by stabilisation of the tumour extent after treatment, and in one patient with partial tumour response.

In eight patients we achieved very good palliative effect. In six of them a decrease in blood pressure was obtained as well as alleviation of headaches, heart

Table III. *Characteristics of patients with SDHB mutation*
Tabela III. *Charakterystyka pacjentów z mutacją SDHB*

Patient number	Progression prior 131-I MIBG treatment	Therapy results	Time to progression after treatment (months)	Follow-up time/survival
1	No	SD	17	Disqualified from chemotherapy because of heart failure and died 32 months after treatment
2	Yes	PD	0	Qualified for external radiotherapy and remains alive 77 months after treatment
3	No	SD	Without progression under surveillance	81 months, still alive

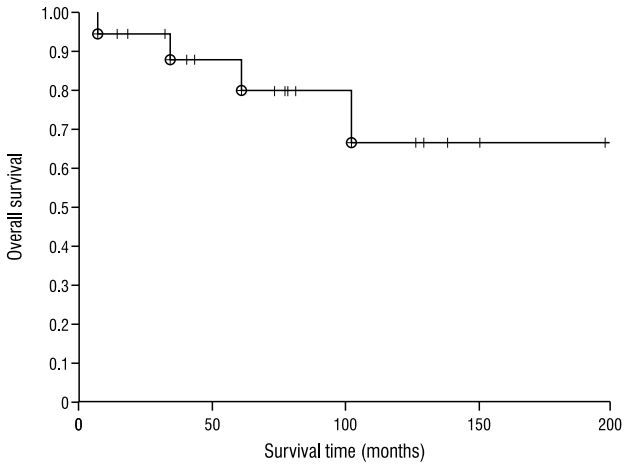

Figure 2. *Kaplan-Meyer survival curve*
Rycina 2. *Krzywa przeżycia Kaplana-Meyera*

palpitations, and weakness. In two patients with massive painful bone metastases the pain was significantly resolved and return of locomotive functions was observed.

In 44% of patients adverse events affecting the haematological system were observed; however, only in 11% of patients they reached the third degree of toxicity according to *Common Terminology Criteria for Adverse Events*, and in all cases except one, they were temporary. In one patient nausea and vomitus occurred during the second course of therapy, treated successfully with metoclopramide and ondansetron. In one patient we observed a short-term exacerbation of arterial hypertension with the need of drug dose adjustment. In spite of thyroid protection, hypothyroidism was observed in almost one third of patients, leading to necessity of levothyroxine substitution. Hypogonadism confirmed by hormonal tests appeared in one female patient. In a young man with varicose veins of spermatic cord, the post therapeutic hormonal data of gonadal axis were normal but azoospermia was diagnosed. Toxicity of the radionuclide treatment is summarised in Table IV.

Table IV. *Summary of 131-MIBG treatment adverse events*
Tabela IV. *Podsumowanie działań niepożądanych leczenia radioizotopowego przy użyciu 131-I MIBG*

Toxicity	No of patients (%)
Haematological	
Leukopaenia	1 (6%)
gr. 1	2 (11%)
gr. 2	1 (6%)
gr. 3	0 (0%)
gr. 4	0 (0%)
Anaemia	
Thrombocytopaenia	
gr . 1	2 (11%)
gr. 2	0 (0%)
gr. 3	1 (6%)
gr. 4	0 (0%)
Hypothyroidism	4 (22%)
Hypogonadism	1 (6%)
Azoospermia and infertility	1 (6%)
Exacerbation of arterial hypertension	1 (6%)
Nausea and vomiting	1 (6%)

Discussion

The rarity of malignant pheochromocytoma and paraganglioma tumours substantially limits the possibility of evaluation of treatment results. Available data referring to the use of 131-I MIBG for treatment of MPPGL in single centres include several series containing 5–49 patients [6, 9–17]. Among these studies only one was a prospective II phase clinical trial [6]. The treatment regimens and doses of radionuclide differ in all series, which hamper comparison. In our Department the mean single dose was 7.25 GBq (196 mCi) and mean cumulative dose 33.08 GBq (894 mCi). Mean cumulative activity in analysed series reported in literature range from 6.9 GBq (186 mCi) to 39.4 GBq (1065 mCi), with the

number of infusions ranging from one to 12 [6, 9–17]. Different criteria assessing tumour response used in different centres are another limitation influencing the comparison of data. Complete response was reported in 0–38% of patients [6, 9–17], and partial response ranged from 17 to 47% [6, 9–17]. Using the RECIST criteria in our study, we observed complete response in two patients (11%) and partial response in another one (6%). This objective tumour response was obtained in MPPGL with metastases localised in bones and lymph nodes. The existing data from a comprehensive review reported by Loh et al. show better response to 131-I MIBG therapy in patients with soft tissue metastases compared with those with bone metastases [18]. This discrepancy is difficult to interpret because we observed only two cases. In our study, in the majority of patients we achieved stabilization of the disease (72%), which is close to the results from other centres in which stable disease was observed in 17–60% of patients [6, 9–17].

In most studies patients were selected to 131-I MIBG therapy independently of disease dynamics. The progressive disease was the inclusion criterion only in one study [16]. In our cohort five patients had confirmed progression prior treatment. In four of them partial response or stable disease was achieved. Differences in opinions about when to initiate the treatment in MPPGL impede the solution of dilemma if stable disease after 131-MIBG treatment is a result of therapy or a consequence of natural tumour behaviour. This limitation also hampers the interpretation of progression-free survival (PFS). The progression-free survival we reported is 85 months. Gedik et al. reported progression-free survival time of 23.1 months [15]. Shilkrut et al. reported PFS of 28.5 months [17]. Only a few studies assessed overall survival (OS). Gonias et al. reported five-year overall survival of 64% in a phase II study of high-dose 131-I MIBG therapy for patients with metastatic pheochromocytoma and paraganglioma [6]. In Rutherford's study five-year overall survival was 68% [19]. In our study five-year overall survival was 87% It is worth to underlining that five-year overall survival for MPPGL patients assessed historically, when radionuclide therapy was not available, was estimated as 44% [20].

There are limited data on the influence of genetic status affecting efficacy of radionuclide treatment. In a study by Gonias et al. 12 patients out of 24 who underwent genetic testing had confirmed SDHB mutation. SDHB-positive patients achieved complete or partial response significantly more often; however, SDHB status was not a significant predictor of overall survival. They concluded that lack of influence on OS despite better response to the treatment may be the result of the aggressive natural behaviour of MPPGL with SDHB mutation [6]. In our group there were three (21%) patients with SDHB mutation. This small number enabled statistical analysis of differences in response to the 131-I MIBG treatment.

In our cohort hormonal response was observed in all patients with elevated metanephrines prior to 131-I MIBG therapy, which was accompanied by stable disease or partial tumour response. Data concerning the influence of hormonal response on overall survival are equivocal. In a phase II study of high-dose 131-I MIBG therapy Gonias et al. reported no predictive value of hormone response to overall survival [6]. In contrast, Safford et al. proved the significance of hormonal response as a predictor of survival [14].

As well as reduction of measurable disease and achieving elongation of progression-free survival, another goal of radionuclide treatment is relieving patients of symptoms. In our cohort 44% of patients benefited and we observed alleviating of catecholamine excess symptoms and complaints related to tumour burden. In a meta-analysis by Loh et al. symptomatic improvement was observed in 76% of patients [18]. In single-centre studies symptomatic response was seen in 50–89% of patients [15, 17, 19, 21].

The most frequent toxicity of 131-I MIBG treatment observed in our study and reported from other centre was haematological. Leukopaenia and thrombocytopaenia affected 50% of our cohort, but mostly there were first- and second-degree temporary events. In studies on the use of similar radionuclide activities, haematological toxicity occurred in 8–40% patients [9–17]. Only in study with high dose 131-I MIBG (median cumulative dose 0.44 GBq (12 mCi/kg) haematological toxicity was severe, affecting more than 80% of patients [6]. Despite the use of sodium perchlorate or potassium iodide for thyroid protection, one third of our patients developed hypothyroidism. In a phase II clinical trial of high-dose 131-I MIBG therapy only 6.1% of patients suffered from hypothyroidism after radionuclide treatment, but in a study by Brans et al. 40% developed hypothyroidism [6, 22]. Temporary increase of blood pressure demanding significant modification of hypotensive therapy was observed by us in one patient during the treatment course, despite the use of alfa-blockers. The same was reported by Sakahara et al. [13]. We did not observe renal failure, which is in line with literature data [6, 9–17].

We report one case of hypogonadism confirmed by hormonal assessment and one case of infertility with ambiguous background. In a phase II clinical trial of high-dose 131-I MIBG therapy, four patients out of 49 developed hypogonadism [6]. Rutherford et al. observed two ovarian failures among a group of 22 patients treated with a median cumulative dose of 20.13 GBq (544 mCi).

Secondary malignancies are rare toxicities after 131-MIBG treatment. Myelodysplasia and acute myelocytic leukaemia were observed with 4% incidence in a study by Gonias with high-dose therapy. In our report there was one case of lymphoma in an 84-year-old female. 131-I MIBG therapy with a cumulative dose of 4.4 GBq (1200 mCi) divided into six courses was her only oncologic treatment besides surgical procedure. Lymphoma appeared four years after radionuclide therapy. Although radiation is a known risk factor for secondary malignancies, its relation to 131-I MIBG treatment is equivocal.

Conclusions

Therapy of malignant pheochromocytoma and paraganglioma is still a challenge. Radionuclide treatment with 131-I MIBG may be an effective form of palliative treatment for patients with inoperative neoplasm spread or progressive disease, or for patients requiring alleviation of symptoms. Toxicity with use of a single dose not exceeding 7.4 GBq (200 mCi) and median cumulative dose below 37 GBq (1000 mCi) is moderate and mostly temporary. The decision of when to initiate the treatment remains under debate.

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