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Title Page

Title:

Safety and efficacy of multiple-dose versus single-dose MIBG therapy in patients with refractory pheochromocytoma and paraganglioma: A single-center retrospective analysis

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Abstract**Objective:**

To investigate the incidence of adverse events (AEs) following single and multiple administrations of I-131 metaiodobenzylguanidine (MIBG) therapy for inoperable pheochromocytomas and paragangliomas (PPGLs).

Methods:

A single-center retrospective study was conducted on patients with inoperable PPGLs who underwent I-131 MIBG therapy between January 2000 and December 2020. A total of 28 patients with available electronic medical records were included. The treatment consisted of a single intravenous administration of 150 mCi (5.55 GBq) of I-131 MIBG. We evaluated the first MIBG treatment and repeated MIBG treatments performed within 200 days of the previous treatment. AEs for each treatment were evaluated using CTCAE version 4.0, and the statistical analysis was conducted at a significance level of $p < 0.05$. Objective response based on RECIST 1.1 criteria and biochemical response based on urinary catecholamines were assessed.

Results:

The study included a total of 63 administrations, consisting of 28 single administrations (SAs), including the first administration for all 28 cases, and 35 multiple administrations

(MAs), which included the second or later administrations. Hematological AEs were evaluable for 23 SAs and 29 MAs. Grade 3 or higher leukopenia occurred in 9.8% of all administrations, and Grade 3 or higher lymphopenia in 23.5%; both were manageable through observation. There were no significant differences in clinical AE Grades 1–2 ($p=0.32$), hematological AE Grades 1–2 ($p=0.22$), or hematological AE Grades 3–4 ($p=0.12$) between MAs and SAs. Statistical analysis for each type of AE revealed significant increases in leukopenia ($p<0.01$) and lymphopenia ($p=0.04$). No significant difference in anemia, thrombocytopenia, or neutropenia was observed between MAs and SAs. There was no significant increase in the incidence rate of Grade 3 or higher hematological AEs for any of the parameters. The objective response rate was 0% for SAs and 36% for MAs. Biochemical response rates were 18% for SAs and 67% for MAs.

Conclusion:

In I-131 MIBG therapy for PPGLs, multiple administrations significantly increased only Grade 1 or 2 lymphopenia and leukopenia compared to single administration.

Keywords: pheochromocytoma, paraganglioma, MIBG, safety, efficacy.

Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors originating from neural crest cells. Those arising from the adrenal medulla are referred to as pheochromocytomas, while those originating outside the adrenal glands from the neural ganglia are known as paragangliomas. Collectively, they are referred to as PPGLs. In the past, they were believed to exist in both malignant and benign forms; however, in the 2017 WHO 4th Classification, all PPGLs were reclassified as non-epithelial malignancies: sarcomas with metastatic potential [1]. Metastatic and recurrent PPGLs are associated with poor prognosis, yet treatment options for inoperable PPGLs remain limited [2].

I-131 metaiodobenzylguanidine (MIBG) therapy is indicated for inoperable PPGLs [3], with typical dosages in Japan ranging from 3.70 to 7.40 GBq (100 to 200 mCi) per treatment [4,5]. However, the reported response rate of I-131 MIBG therapy is quite low at 5.9% [6]. It is known that adverse events (AEs) are mild with low-dose administration ranging from 3.70 to 5.55 GBq (100 to 150 mCi) [7–9]. On the other hand, high-dose therapy (492 to 1160 mCi per dose) has been shown to improve the response rates but is accompanied by severe AEs, including hematologic toxicity requiring autologous stem cell transplantation [10]. As a method to enhance the response rates, high-

specific-activity MIBG (Azedra®) has been administered in some overseas settings (maximum 500 mCi per dose), but it still carries a high risk of severe hematologic toxicity [11]. Van Hulsteijn et al. reported in a systematic review that Grade 3 or higher neutropenia or thrombocytopenia are the most frequently observed severe AEs in I-131 MIBG therapy [12]. However, especially in Japan, facilities capable of administering high doses are limited due to legal regulations. Therefore, in many facilities in Japan, it is necessary to administer multiple low doses to enhance therapeutic response. For neuroendocrine tumors, it has been reported that three administrations (150 mCi) of MIBG treatment result in an improved response rate of 27.3% [13]. Nevertheless, while multiple administrations of I-131 MIBG are expected to provide better therapeutic outcomes, it remains unclear whether the incidence of AEs is increased by a multiple-dose administration protocol.

This study aims to investigate the safety and efficacy differences between single and multiple administrations of I-131 MIBG therapy in inoperable PPGLs.

Methods

This retrospective study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and approved by the Human Research

Ethics Committee of the Hokkaido University Graduate School of Medicine and the Institutional Review Board of Hokkaido University Hospital (#022-0329). Written informed consent was waived because of the retrospective nature of the study.

This study focused on the 28 patients for whom image data and clinical information were available in electronic medical records among the 38 patients of inoperable PPGL treated with I-131 MIBG therapy at Hokkaido University Hospital between January 2000 and December 2020, as previously reported [14,15]. Specifically, we evaluated a total of 63 administrations, including the first MIBG treatment and repeated MIBG treatments performed within 200 days of the previous treatment. Information regarding AEs was available for all 28 patients (63 administrations). Hematological AEs were assessed through blood tests and were documented for a total of 23 cases and 52 administrations. Response Evaluation Criteria in Solid Tumors (RECIST) [16] evaluations based on image data were possible for 24 patients, while biochemical evaluations through urine tests were conducted for 27 cases.

I-131 MIBG therapy and imaging

I-131 MIBG was administered at a dose of 5.55 GBq (150 mCi) per administration, given by continuous intravenous infusion through a peripheral vein over 60 minutes

[2,17]. Patients who tolerated the treatment were given multiple treatments. If severe myelosuppression occurred, a dose reduction to 3.70 GBq (100 mCi) or discontinuation was to be considered [14,15]. Potassium iodide was orally administered as a thyroid protective measure. Once administered I-131 MIBG, the patients were isolated in a dedicated room for unsealed radioactive drugs until they met the release criteria set by the applicable Japanese regulations. Whole-body planar imaging and single photon emission computed tomography/computed tomography were conducted after release.

Evaluation items

The data including baseline characteristics, hormone levels, urinary catecholamine levels, treatment history, first and best objective response to I-131 MIBG, and past treatment history (chemotherapy, surgery, external irradiation, transcutaneous arterial embolization, radiofrequency ablation) were collected from medical records as assessment parameters. High urinary catecholamine levels were defined as a significant increase of more than three times the upper limit. The reference values were set at Hokkaido University Hospital.

Adverse events evaluation

AEs that could be collected from the electronic health records were evaluated using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [18]. Patients' subjective complaints and objectively assessable physical symptoms were defined as clinical AEs. Clinical AEs were assessed during inpatient care, both before and after treatment, as well as during outpatient visits before and after hospitalization. Hematological AEs were evaluated based on blood test data during inpatient care and outpatient visits before and after hospitalization.

Complaints, physical findings, and hematological abnormalities present prior to treatment initiation were not considered treatment-related AEs. Each AE was classified according to CTCAE version 4.0.

Response evaluation

Biochemical efficacy was assessed in patients with high urinary catecholamine levels based on the percentage change in catecholamine concentrations in urine, as follows [6]:

- CR (Complete Response): Catecholamine concentrations in urine remained within the normal range.

- PR (Partial Response): Catecholamine concentrations in urine decreased by 50% or more.
- PD (Progressive Disease): Catecholamine concentrations in urine increased by 25% or more.
- SD (Stable Disease): None of the above criteria were met.

Objective response was assessed by two radiologists based on RECIST version 1.1. For the RECIST 1.1 criteria, patients were graded as a complete response (CR), a partial response (PR), stable disease (SD), or progressive disease (PD). Notably, if the lesion had a small soft tissue component (less than 1 cm) by cross-sectional imaging techniques such as CT or MR, it was deemed to be non-measurable and recorded as a non-target lesion according to RECIST 1.1. Non-contrast CT was primarily used for imaging evaluation, with contrast CT, MIBG SPECT/CT, or FDG PET/CT information also referenced when available.

Data analysis

Categorical data were presented as absolute numbers and relative frequencies (percentages), whereas continuous data were presented as median and range. Each AE

was classified as Grade 1–2 or Grade 3–4 according to CTCAE version 4.0. No patients were categorized as having a Grade 5 AE. Statistical analysis was conducted using JMP® Pro version 17.0.0 (SAS Institute Japan, Tokyo). All the administrations were categorized into either the single administration group (SAs) or multiple administrations group (MAs). The AEs and responses after the first administration in all cases were included in the SAs, and those after the second or later administrations in all cases were included in the MAs. That is, for cases with three administrations, AE and the responses of the first administration were included in the SAs, and those of the second and third administrations were included in the MAs. Three patients had received I-131 MIBG therapy at other hospitals before their initial treatment at our hospital. Since this study focused on AEs caused by repeated treatment at short intervals, we considered that a sufficient interval had passed for the three cases with a history of I-131 MIBG therapy at other hospitals (9 months, 27 years, and 1 year ago, respectively). Therefore, we decided not to include the treatment histories from other hospitals in the analysis. We defined the initial treatment at our hospital as the first treatment and included it in the SAs. The efficacy and safety of these two groups were compared using Fisher's exact test (one-tailed). Furthermore, regarding the impact on hematologic AEs due to cumulative administered dose, the administrations were divided into two groups based on the cumulative administered dose at

administration: those with a cumulative administered dose of 11.1 GBq (300 mCi) or less, and those exceeding 11.1 GBq (300 mCi), and Fisher's exact test was conducted. The significance level was set at $p < 0.05$.

Results

The patient demographics are presented in Table 1. The total number of cases was 28, with 10 (36%) being male and 18 (64%) being female. Eighteen of the patients (64%) had pheochromocytoma and 10 (36%) had paraganglioma. Among the patients receiving their initial MIBG treatment at our institution, prior treatment history included surgery in 27 patients (96%), chemotherapy in 10 patients (36%), external radiation therapy in 10 patients (36%), transcutaneous arterial embolization in 1 patient, and radiofrequency ablation in 2 patients, and 3 patients had a history of MIBG treatment at other institutions. Evaluable lesions by imaging assessment included primary tumors in 2 cases (7%), lymph node metastases in 7 cases (25%), lung metastases in 12 cases (43%), liver metastases in 10 cases (36%), bone metastasis in 14 cases (50%) and peritoneal metastases in 7 cases (25%). The total number of administrations analyzed was 63: 28 first administrations, 21 second administrations, 13 third administrations, and 1 fourth administration. Thus, the SAs had 28 administrations and the MAs had 35 administrations. The

median interval between treatments was 98 days (range: 42–189). The reasons for the treatment interval exceeding 200 days or treatment discontinuation were as follows: stable disease in 11 cases, disease progression in 5 cases, bone marrow suppression in 4 cases, absence of evident accumulation in post-treatment scintigraphy in 3 cases, additional external irradiation in 3 cases, additional surgery in 1 case, and treatment discontinuation due to other illnesses in 1 case.

Adverse events

Clinical AEs were assessable for 28 (100%) administrations in the SAs and 35 (100%) in the MAs. Hematological AEs were assessable in 23 (82.1%) administrations in the SAs and 29 (82.9%) administrations in the MAs. Clinical AEs of Grades 1–2 and Grades 3–4 were observed following 75.0% (21/28) and 0.0% (0/28) of administrations in the SAs, respectively, while hematological AEs of Grades 1–2 and 3–4 were seen in 60.9% (14/23) and 21.7% (5/23) of administrations in this group, respectively. For the MAs, clinical AE Grades 1–2 and Grades 3–4 were 82.9% (29/35) and 0.0% (0/35) of the total administrations, respectively, and hematological AE Grades 1–2 and Grades 3–4 accounted for 75.9% (22/29) and 41.4% (12/29), respectively. There were no significant differences in clinical AE Grades 1–2 ($p=0.32$), hematological AE Grades 1–2 ($p=0.22$),

or hematological AE Grades 3–4 ($p=0.12$) (Fig. 1). Statistical analysis for each type of AE revealed significant increases in leukopenia ($p<0.01$) and lymphopenia ($p=0.04$) (Fig. 2). No significant increases in AEs were observed in other categories. There was no significant increase in the incidence rate of Grade 3 or higher hematological AEs for any of the parameters (leukopenia: $p=0.56$; lymphopenia: $p=0.22$; anemia: $p=0.78$; thrombocytopenia: $p=0.54$) (Fig. 3). The relationship between total dose and hematological AEs was analyzed with 52 administrations in 27 patients for whom hematological data were available, except for one patient for whom the dose was unknown. These were divided into two groups based on total dose at the time of administration: those at or below 11.1 GBq (300 mCi) (39 administrations) and those above 11.1 GBq (300 mCi) (13 administrations). However, there were no statistically significant differences in the incidence of all Grade and Grade 3-4 hematologic AEs (leukopenia, lymphopenia, neutropenia, anemia, and thrombocytopenia) (Table 3).

Urinary catecholamines response

The results of the urinary catecholamine analysis are summarized in Figure 4. Urinary catecholamine levels were evaluable in a total of 27 cases (adrenaline: $n=27$ cases; noradrenaline: 27; dopamine: 25; metanephrine: 18; normetanephrine: 18). High

urinary catecholamine levels were observed in 15 cases. Specifically, an increase in adrenaline was observed in 2 out of 15 cases (13%), in noradrenaline in 11 out of 15 cases (73%), in dopamine in 1 out of 15 cases (7%), in metanephrine in 4 out of 15 cases (27%), and in normetanephrine in 12 out of 15 cases (80%). Response assessments for urinary catecholamines were evaluable in 11 out of 28 cases after the initial treatment, and in 9 out of 21 patients who underwent multiple treatments, it was possible to evaluate the response after the final treatment. The median number of days from the treatment date to the examination date for the assessment after the initial treatment was 104 (range: 62–287 days). Similarly, for the assessment after multiple treatments, the median number of days from the treatment date to the examination date was 104 (range: 90–1163 days). Following the initial treatment evaluation, there were no complete responses (CR), 2 cases with PR (18%), 7 cases with SD (64%), and 2 cases with PD (18%). After the evaluation following multiple treatments, there were no cases with CR, 6 cases with PR (67%), 2 cases with SD (22%), and 1 case with PD (11%). The response rate after the initial treatment was 18%, while after multiple treatments, it increased to 67%.

Objective response

Following the initial treatment evaluation, among the 24 (85.7%) cases under assessment, there were no cases with CR or PR, 20 cases with SD (83%), and 4 cases with PD (17%). After the evaluation following multiple treatments, among the 14 (50.0%) cases under assessment, there were no cases with CR, 5 cases with PR (36%), 6 cases with SD (43%), and 3 cases with PD (21%) (Fig. 5).

Discussion

Compared to the first administration, leukopenia and lymphopenia were significantly increased after the second and consecutive administrations. Leukopenia showed a significant increase in Grade 1–2, with no significant increase in Grade 3–4. In all cases, leukopenia was manageable through observation. Additionally, lymphopenia exhibited a trend of increase in both Grade 1–2 and Grade 3–4, but there was no statistically significant increase in either group. The limited number of cases may explain the lack of statistical significance, but clinically, there were no significant lymphopenia issues in any of the cases, and all cases were manageable through observation. Neutropenia, anemia, and thrombocytopenia did not exhibit a significant increase. In cases of leukopenia, the clinical concern primarily lies in neutropenia, with severe neutropenia predisposing individuals to febrile neutropenia due to increased susceptibility to infections. However, none of

the patients in this study required administration of granulocyte colony-stimulating factor products, even when MIBG was administered consecutively at a median interval of 98 days.

In the Japanese Phase 2 clinical trial (200 mCi single injection), CTCAE Grade 3 or higher hematological AEs were observed in 31% (5/16) of cases [6], which was generally consistent with the 23% (12/52) observed in this analysis. However, in the Japanese Phase 2 clinical trial, no hematological AEs other than lymphopenia were observed, while in this analysis, there were a few cases with Grade 3 or higher AEs, including leukopenia in 19% (10/52), anemia in 6% (3/52), and thrombocytopenia in 8% (4/52) of the administrations. The reason for this difference could be attributed to the fact that this analysis included cases with longer duration after disease onset, who had undergone various treatments, and their overall health status had deteriorated.

In addition, when comparing the incidence and severity of hematological AEs with high-dose therapy or HSA-MIBG therapy [11,19], it is evident that the degree and frequency of AEs were lower in this study. In a Phase 2 study of high-dose therapy for metastatic PPGL overseas [10], Grade 3 or higher hematological AEs were observed in 85% for leukopenia, 87% for neutropenia, 83% for thrombocytopenia, and 8% for anemia. The frequency of hematological AEs other than anemia is clearly higher following high-

dose therapy. In this analysis, the total administered dose for multiple-dose administration ranged from 11.1 to 22.2 GBq (300–600 mCi), which is lower when compared to the total administered dose of 492 to 1160 mCi for high-dose therapy or HSA-MIBG therapy, yet the degree and frequency of AEs were notably lower. On the other hand, Kotecka et al. reported that AEs remained moderate and temporary as long as the total administered dose did not exceed 200 mCi per session and the cumulative dose was below 1000 mCi [20]. Moreover, one report indicated that even with a single dose of approximately 200 mCi in low-dose administration, patients with a cumulative dose of 800 mCi experienced Grade 3 or higher hematological AEs [21]. In the same report, severe hematological AEs were observed when the cumulative dose reached 793 mCi (4 treatments). However, some reports include cases demonstrating tolerance to higher doses [22]. Administering multiple low doses reduces the occurrence of AEs compared to a single dose with an equivalent cumulative dose. However, as the cumulative dose increases, there is an implication of an increase in the occurrence of severe AEs. This study involved fractionated administration with a maximum cumulative dose of 600 mCi albeit at relatively short intervals, and the absence of severe AEs aligns with previous reports. We examined the occurrence rates of hematological AEs in the group with a total administered dose of 11.1GBq

(300mCi) or less and the group exceeding 11.1GBq (300mCi), but no significant difference was observed. This result is consistent with previous studies [20,21].

The most frequently observed adverse event was nausea, but cases of vomiting were limited, and most cases were managed through observation or antiemetic administration. Clinical observations associated with excessive catecholamine release, such as increased sweating, headache, tachycardia, and hypertension, were also noted, but there was no significant difference between the SAs and MAs.

To summarize our findings on AEs, multiple-dose administration was associated with a significant increase in leukopenia and lymphopenia in Grade 1–2 compared to single-dose administration. There were no clinically significant cases and there was no statistically significant difference in the incidence of other AEs.

The response rate of urinary catecholamines after the initial treatment was 18%, but in the assessment following multiple treatments, the response rate reached 67%. For 2 patients, the period from the treatment date to the examination date was relatively prolonged at 497 days and 1963 days, respectively. The response was SD for one of these patients and PR for the other, and no further treatment was required before the examination. In terms of objective response, the response rate was 0% after the initial treatment, but after multiple treatments, a response rate of 36% was achieved. In a Japanese Phase

2 clinical trial, the urinary catecholamine response was reported to be 23.5%, and the objective response was 5.9% [6], which is generally consistent with the response rate after the initial treatment in this study. However, it should be noted that patients with favorable outcomes often continued with multiple treatments, while those whose conditions deteriorated were more likely to discontinued multiple treatments. Furthermore, the fact that the treatment efficacy was determined within 200 days of the first dose could have led to an underestimation of treatment efficacy, since this is a relatively early time point. Therefore, comparing response rates after the initial treatment and after multiple treatments in this study is challenging. However, among the 5 patients for whom evaluable data were available for the initial and each subsequent treatment, 4 patients achieved a better treatment effect by continuing with treatment (Fig. 6).

In conclusion, in I-131 MIBG therapy, multiple treatments led to a significant increase in lymphopenia and leukopenia, but no significant increase was observed in other AEs. The observed lymphopenia and leukopenia were not clinically severe and were manageable through observation. On the other hand, the possibility of achieving better treatment outcomes through multiple treatments was suggested. For patients who demonstrated tolerability after the initial treatment, continuing with subsequent treatments was suggested to yield better treatment effects without increasing significant adverse events.

As a limitation of this study, currently in Japan, the standard practice for I-131 MIBG therapy involves a single dose of 7.40GBq (200mCi). It is important to note that the dose used in this retrospective single-center study, 5.55GBq (150mCi) per treatment, differs from this standard dosage. Consequently, there is a need to be cautious regarding the potential for an increased incidence of AEs when 7.40GBq (200mCi) was administered.

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Disclosure

The authors have no potential conflicts of interest related to the content of this paper.

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Table 1 Patient characteristics**Table 2** Treatment-related Adverse events

Table 3 A test on the occurrence rates of hematological adverse events (AEs) (leukopenia, neutropenia, lymphopenia, anemia, thrombocytopenia) between the group with a total administered dose of 11.1GBq (300mCi) or less and the group exceeding 11.1GBq (300mCi) at the time of administration. The total administered dose includes doses administered at other hospitals. One case for which dosage information from other institutions was not available was excluded.

Table 4 Response of urinary catecholamines and objective response

Objective response was assessed based on RECIST 1.1 criteria. Biochemical response based on urinary catecholamines were assessed as follows: CR (Complete Response): Catecholamine concentrations in urine remained within the normal range. PR (Partial Response): Catecholamine concentrations in urine decreased by 50% or more. PD (Progressive Disease): Catecholamine concentrations in urine increased by 25% or more. SD (Stable Disease): None of the above criteria were met.

Figure Legends

Fig. 1 Comparison of the incidence rates of adverse events (AEs) between single administrations and multiple administrations

No cases developed clinical AEs of Grades 3–4.

Fig. 2 Comparison of the incidence rates of each type of adverse events (AEs) between single administrations (left bar) and multiple administrations (right bar) treatments

Fig. 3 Comparison of the incidence of hematological adverse events (AEs) by Grade between single administrations (SAs) and multiple administrations (MAs)

The left bar of each category represents SAs, while the right bar represents MAs. We conducted tests for the incidence rate of Grade 3 or higher AEs for each item.

Fig. 4 (a) Change from baseline in urinary catecholamine levels after first administration (n= 11) **(b)** Change from baseline in urinary catecholamine levels after multiple administrations (n= 9)

For patients exhibiting significant increases in multiple catecholamines, the presentation focused on the catecholamine with the most notable elevation rate from the upper limit of the baseline values in the pre-treatment assessment.

Fig. 5 (a) Change from baseline in the target lesion on RESIST after first administration (n= 24) **(b)** Change from baseline in the target lesion on RESIST after multiple administrations (n= 14)

Fig. 6 Changes in catecholamine levels from baseline in 5 cases where evaluation of urinary catecholamines was possible after each treatment session

The type of catecholamine displayed was the one that exhibited the most significant increase prior to treatment.

Table 1 Patient characteristics

Characteristic	Data	Percentage
Patient	28	
Male	10	36%
Female	18	64%
Diagnosis		
Pheochromocytoma	18	64%
Paraganglioma	10	36%
Age at the diagnosis of the refractory PPGLs		
Median (years)	54 (22-84)	
Number of treatments each patient received		
1	7	25%
2	8	29%
3	12	43%
4	1	4%
Reasons for Extended Treatment Intervals or Treatment Discontinuation		
Disease stability	11	39%
Disease exacerbation	5	18%
Bone marrow suppression	4	14%
No remarkable uptake	3	11%
Addition of external Irradiation	3	11%
Addition of surgery	1	4%
Other disease	1	4%
Previous treatment before MIBG		
Surgery	27	96%
Chemotherapy	10	36%
Irradiation	10	36%
Transcatheter Arterial Embolization	1	4%
Radiofrequency ablation	2	7%
Target lesion		
Primary lesion	2	7%
Lymphnode	7	25%
Lung metastasis	12	43%

Liver metastasis	10	36%
Bone metastasis	14	50%
Peritoneal metastasis	7	25%

Table 2 Treatment-related Adverse events

	Single Administration (n = 28)		Multiple Administration (n = 35)		p value
Clinical AEs	(n = 28)		(n = 35)		
Nausea	19	67.9%	26	74.3%	0.388
Vomiting	4	14.3%	2	5.7%	0.944
Headache	4	14.3%	8	22.9%	0.298
Palpitations	2	7.1%	1	2.9%	0.918
Sweating	3	10.7%	4	11.4%	0.626
Tachycardia	1	3.6%	2	5.7%	0.584
Bradycardia	0	0.0%	1	2.9%	0.556
Hypertension	1	3.6%	1	2.9%	0.305
Orthostatic hypotension	0	0.0%	2	5.7%	0.316
Taste disturbance	2	7.1%	5	14.3%	0.556
Fever	0	0.0%	1	2.9%	0.807
Hematological AEs	(n = 23)		(n = 29)		
Leukopenia	9	39.1%	21	72.4%	0.007
Neutropenia	1	4.3%	2	6.9%	0.559
Lymphopenia	7	30.4%	16	55.2%	0.040
Anemia	6	26.1%	7	24.1%	0.639
Thrombocytopenia	7	30.4%	8	27.6%	0.617

Table 3

	AEs of all Grades					AEs of Grade 3–4				
	$\leq 300\text{mCi}$ (n= 39)		300mCi < (n= 13)		p value	$\leq 300\text{mCi}$ (n= 39)		300mCi< (n= 13)		p value
Leukocytopenia	20	51%	10	77%	0.10	2	5%	3	23%	0.09
Neutropenia	2	5%	1	8%	0.59	0	0%	0	0%	–
Lymphopenia	17	44%	6	46%	0.56	9	23%	3	23%	0.64
Anemia	9	23%	6	46%	0.11	2	5%	0	0%	0.56
Thrombocytopenia	8	21%	5	38%	0.18	3	8%	0	0%	0.41

Table 4

	Urinary catecholamines response				Objective response			
	Single Ad- ministrations (n=11)		Multiple Ad- ministra- tions (n=9)		Single Ad- ministra- tions (n=24)		Multiple Ad- ministra- tions (n=14)	
CR	0	0%	0	0%	0	0%	0	0%
PR	2	18%	6	67%	0	0%	5	36%
SD	7	64%	2	22%	20	83%	6	43%
PD	2	18%	1	11%	4	17%	3	21%
Re- sponse rate	18%		67%		0%		36%	

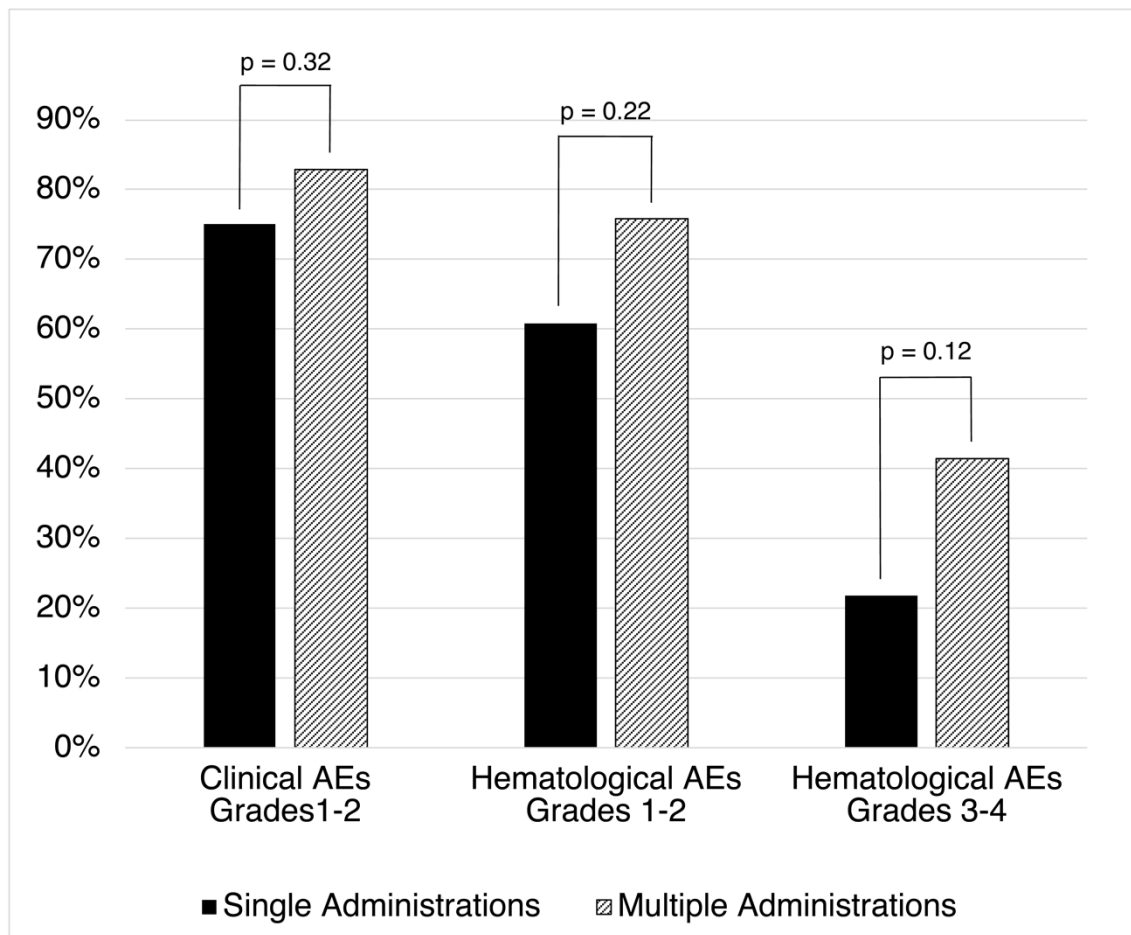
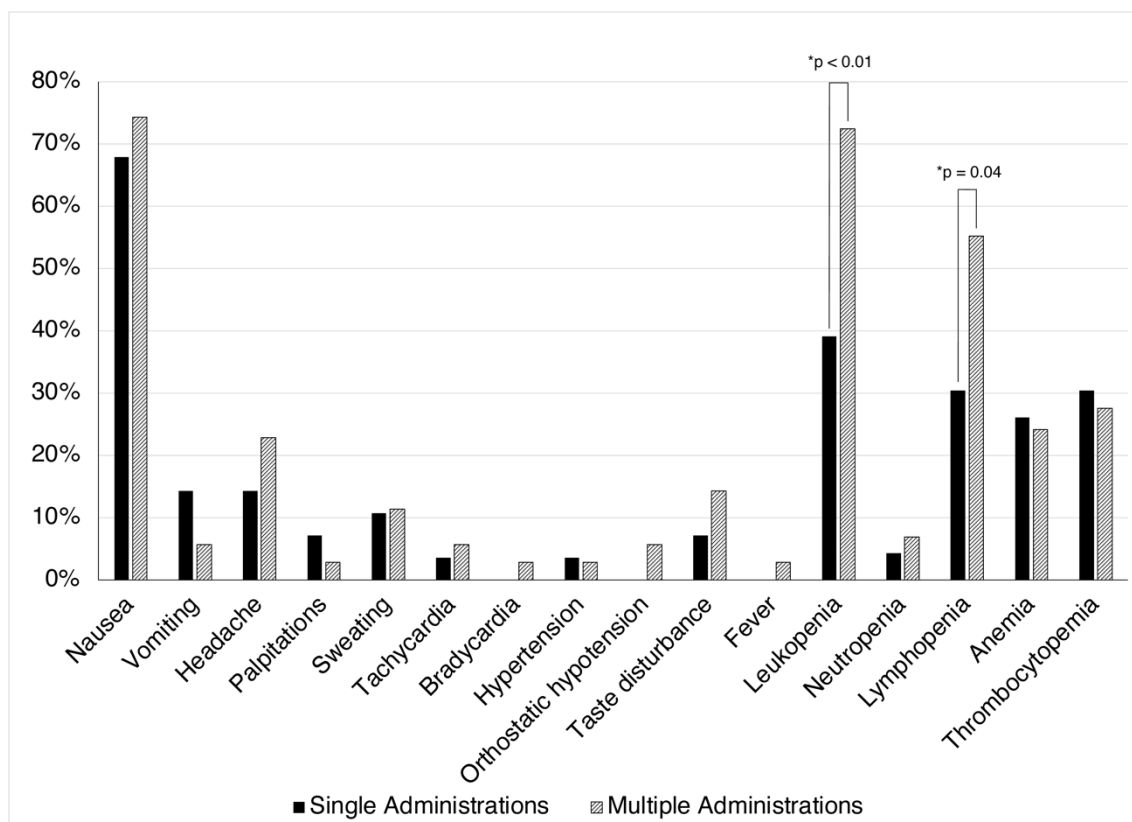


Figure 1

**Figure 2**

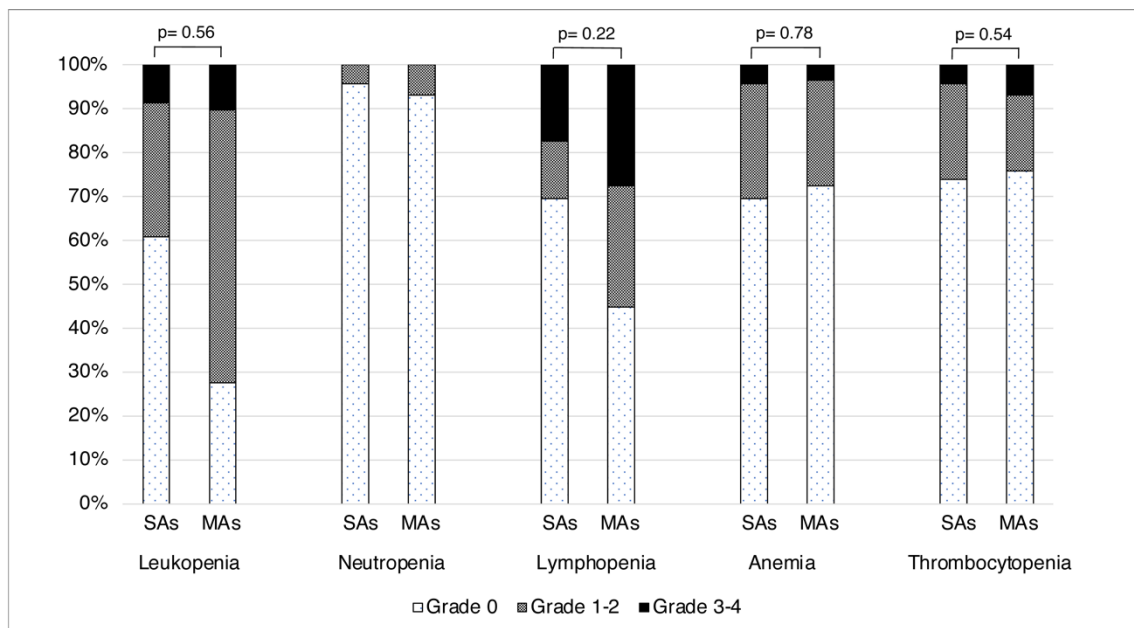


Figure 3

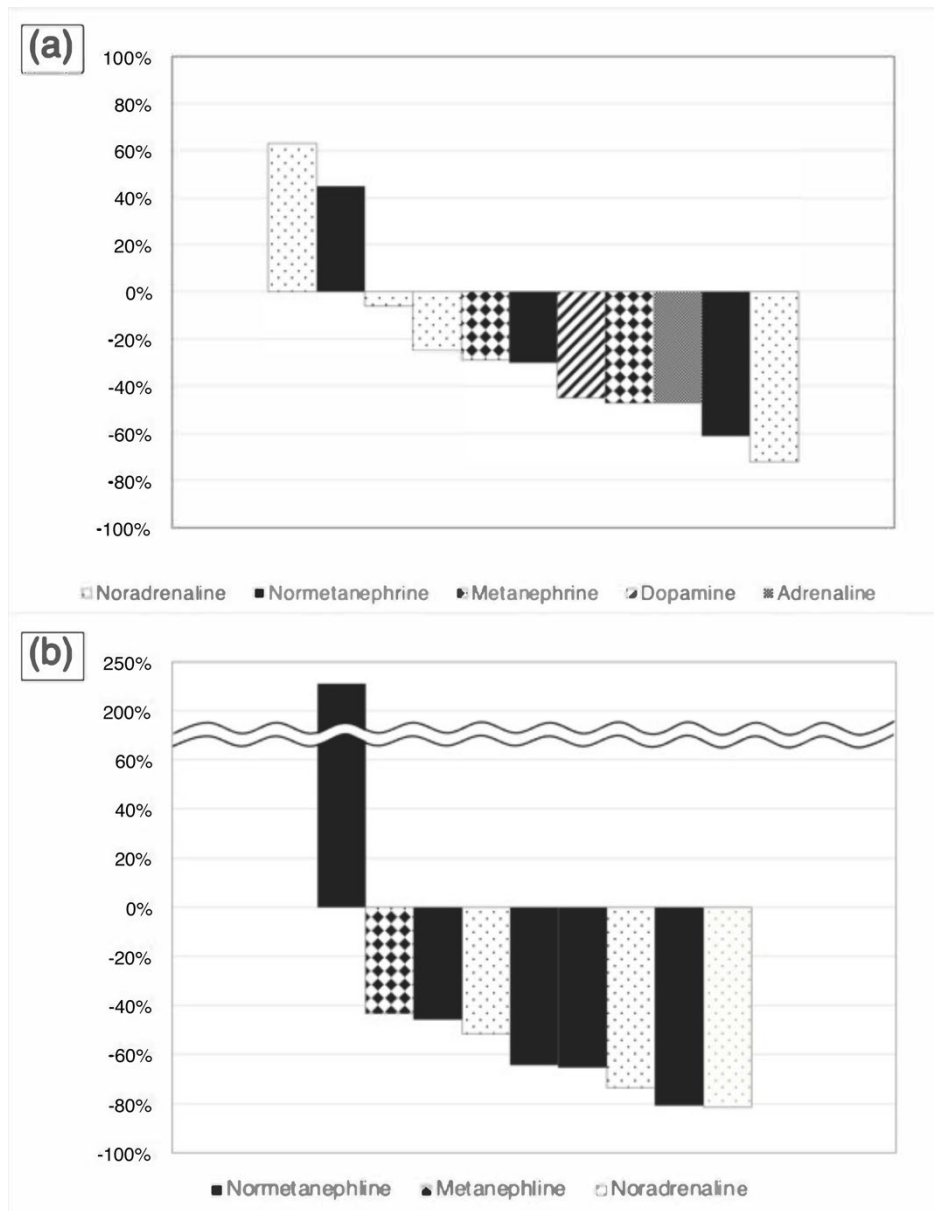


Figure 4

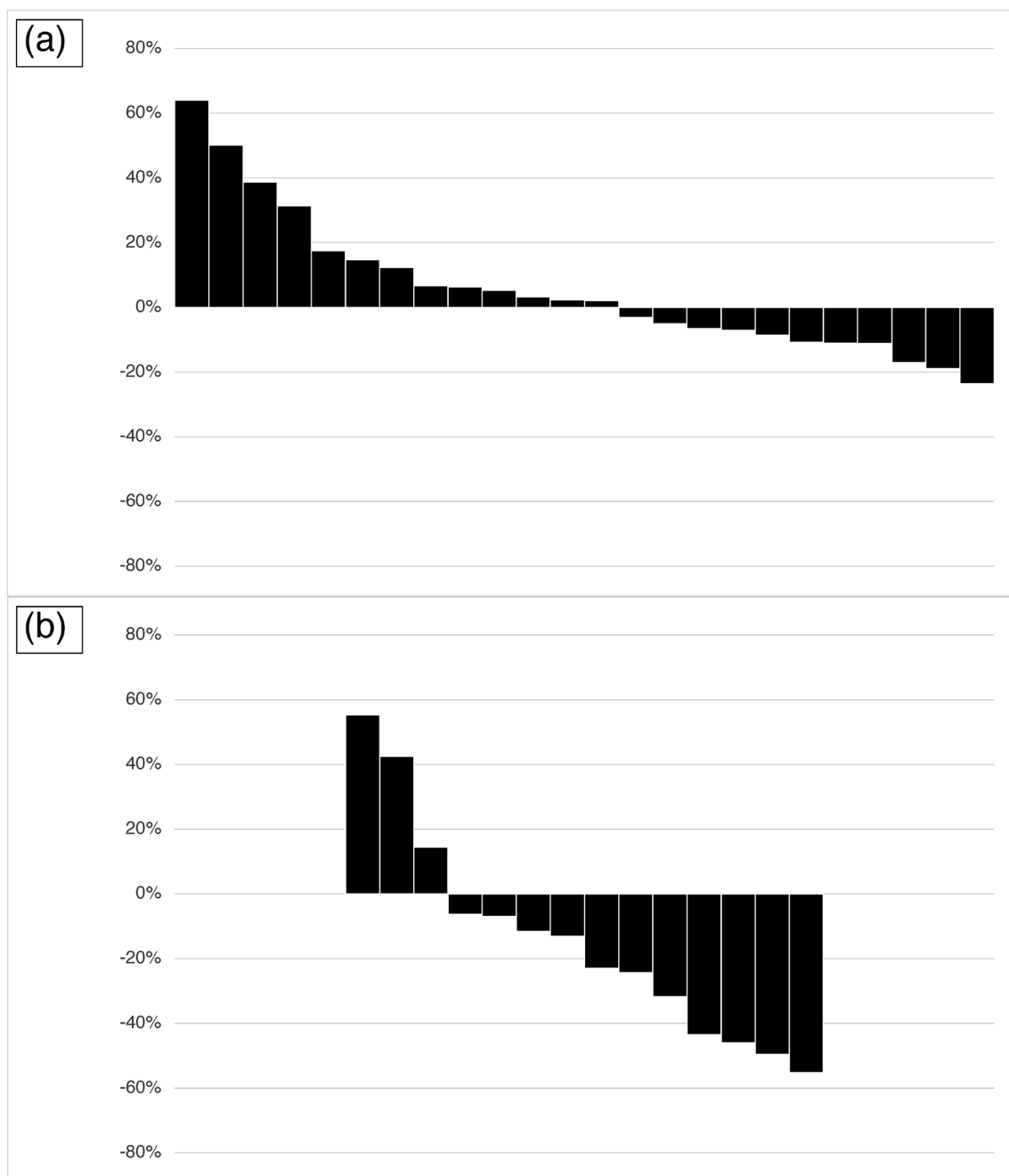
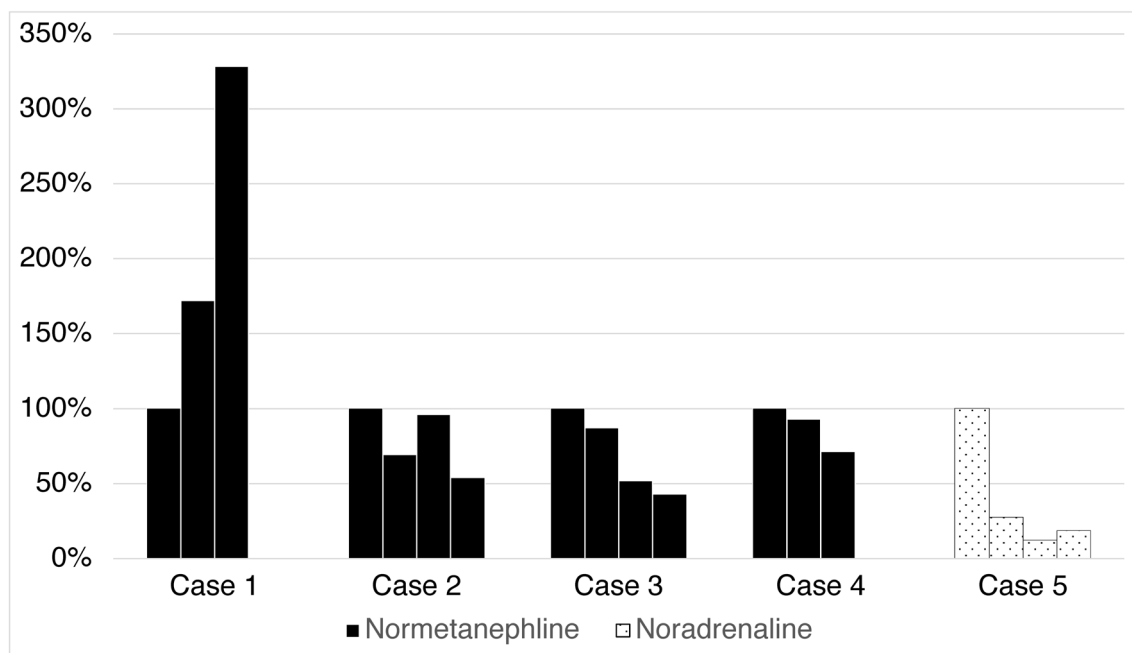


Figure 5

**Figure 6**