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MIRTAZAPINE COMBINED WITH DOUBLET THERAPY FOR THE PREVENTION OF CARBOPLATIN-INDUCED NAUSEA AND VOMITING IN PATIENTS WITH THORACIC MALIGNANCIES

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ABSTRACT

Introduction: Carboplatin is classified as an anticancer agent with emetic potential at the high end of the moderate category, depending on the dose. Mirtazapine blocks 5-hydroxytryptamine type (5-HT)2A, 5-HT2C, 5-HT3 and histamine H1 receptors, similarly to olanzapine. We evaluated the efficacy and safety of mirtazapine with doublet therapy for carboplatin-induced nausea and vomiting in patients with thoracic malignancies.

Methods: We conducted a prospective, open-label, single-arm, multicenter, phase II trial in four centers in Japan. Patients who received a carboplatin (AUC ≥ 4)-based regimen and had never been administered moderate or high emetogenic chemotherapy were eligible. All patients received mirtazapine (15 mg p.o. daily on days 1–4, at bedtime) in combination with granisetoron (1 mg i.v. 30 minutes before chemotherapy on day 1) and dexamethasone (9.9 mg i.v. or 12 mg p.o. 30 minutes before chemotherapy on day 1 and 6.6mg i.v. or 8 mg p.o. on days 2–3). The primary endpoint was complete response (CR: defined as no emesis and no use of rescue medication) rate during the delayed period (24–120 hours). A total of 46 patients were required to detect a 15% improvement in CR from 69% to 84% with a one-sided type I error of 0.1 and 80% power. As some study dropouts were expected, we set the target sample size to 51 patients.

Results: Between July 2022 and July 2023, 52 patients were enrolled. 48 patients who met criteria were included in efficacy and safety analysis. The CR rate in the delayed phase was 83.3% (95% CI, 71.9–100%, p=0.019). The CR rate in the acute (0–24 hours) and overall phases (0–120 hours) were 100% and 83.3%, respectively. No grade 3 or higher adverse events were observed with mirtazapine except for dry mouth (n=1, 2.1%).

Conclusions: Mirtazapine combined with doublet therapy is effective at preventing nausea/vomiting and is well tolerated.

INTRODUCTION

- **Carboplatin is a key drug in treating thoracic malignancies. Its emetic potential appears to be at the high end of the moderate category. Recent guidelines recommend a triplet antiemetic regimen (5-HT3 receptor antagonist, dexamethasone, and NK1 receptor antagonist) for preventing carboplatin-induced nausea and vomiting.**
- **Mirtazapine, an antidepressant, blocks multiple receptors (5-HT2A, 5-HT2C, 5-HT3, and H1) similar to olanzapine. Mirtazapine has a favorable safety profile, especially in elderly and diabetic patients.**
- **This study aimed to evaluate the efficacy and safety of mirtazapine, granisetron, and dexamethasone for preventing CINV in patients with thoracic malignancies receiving carboplatin-based chemotherapy (AUC ≥ 4 mg/mL per minute).**

METHODS AND MATERIALS

Study design: open-label, single-arm, multicenter, phase II trial

Figure 1. Protocol treatment

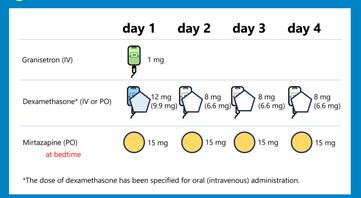
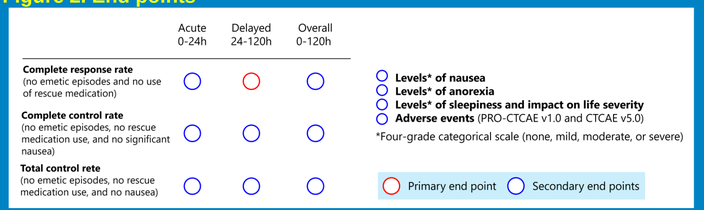


Figure 2. End points



Key eligibility criteria:

- **Diagnosis of thoracic malignancies and scheduled to receive CBDCA-based chemotherapy (AUC ≥ 4)**
- **Aged 20–79 years at time of enrollment**
- **Eastern Cooperative Oncology Group performance status of 0–2**

Data collection

- **The data was collected from patients' diaries**
- **The daily diary began on day 1 of chemotherapy and entries were made over a 5-day period**

Statistical methods

Sample size: 51 (Null hypothesis: 69%, An alternative hypothesis: 84%, One-sided alpha: 0.1, Power: 80%, Assumed drop-out rate: 10%)

RESULTS

Enrollment period: Between July 2022 and July 2023

Figure 3. Trial profile

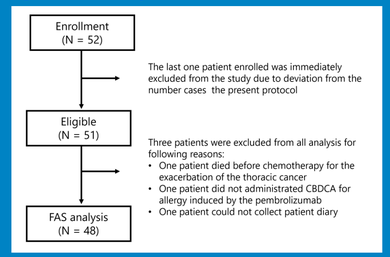


Table 2. Rate of CR, CC, and TC in the delayed, overall, and acute periods

	Acute phase			Delayed phase			Overall phase		
	N (%)	95% CI	*p* value	N (%)	95% CI	*p* value	N (%)	95% CI	*p* value
Complete response	48 (100)	0.939 – 1.00	< 0.001	**40 (83.3)**	**0.719 – 1.00**	**0.019**	40 (83.3)	0.719 – 1.00	0.019
Complete control	48 (100)	0.939 – 1.00	< 0.001	40 (83.3)	0.719 – 1.00	0.019	40 (83.3)	0.719 – 1.00	0.019
Total control	47 (97.9)	0.905 – 1.00	< 0.001	35 (72.9)	0.604 – 1.00	0.34	35 (72.9)	0.604 – 1.00	0.34

Treatment-related adverse events evaluated by CTCAE ver.5.0: No grade 3 or higher treatment-related adverse events were observed, except for one patient who experienced grade 3 dry mouth.

Table 1. Patient characteristics

Number of patients	48		
Age, yr, median (range)	72 (66–74)	Carboplatin dose, n (%)	
Gender, n (%)		AUC 4 mg/mL/min	5 (10.4)
Female	4 (8.3)	AUC 4.5 mg/mL/min	1 (2.1)
Male	44 (91.7)	AUC 5 mg/mL/min	36 (75.0)
ECOG PS, n (%)		AUC 6 mg/mL/min	6 (12.5)
0	27 (56.3)	Additional anticancer drugs, n (%)	
1	19 (39.6)	Etoposide	1 (2.1)
2	2 (4.2)	Etoposide + Durvalumab	7 (14.6)
Thoracic cancer, n (%)		Nab-paclitaxel	5 (10.4)
Small cell lung cancer	8 (16.7)	Nab-paclitaxel + Atezolizumab	2 (4.2)
Non-small cell lung cancer	40 (83.3)	Nab-paclitaxel + pembrolizumab	8 (16.6)
Combination of radiotherap, n (%)		Paclitaxel + bevacizumab + Atezolizumab	2 (4.2)
Yes	4 (8.3)	Paclitaxel + Ipilimumab + nivolumab	2 (4.2)
No	44 (91.7)	Paclitaxel+pembrolizumab	3 (6.2)
Diabetes mellitus, n (%)		Pemetrexed	1 (2.1)
Yes	14 (29.2)	Pemetrexed + Ipilimumab + nivolumab	1 (2.1)
No	34 (70.8)	Pemetrexed + pembrolizumab	11 (22.9)
Habitual alcohol consumption, n (%)		Vinorelbine	5 (10.4)
Yes	18 (37.5)		
No	30 (62.5)		
Motion sickness, n (%)			
Yes	3 (6.3)		
No	45 (93.8		
Morning sickness, n (%)			
Yes	1 (2.1)		
No	9 (18.8)		
No experience	38 (79.2)		
Unknown	0		

Figure 3: Somnolence

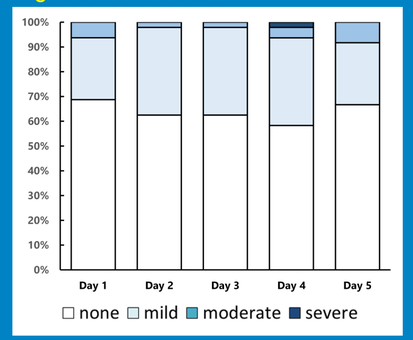
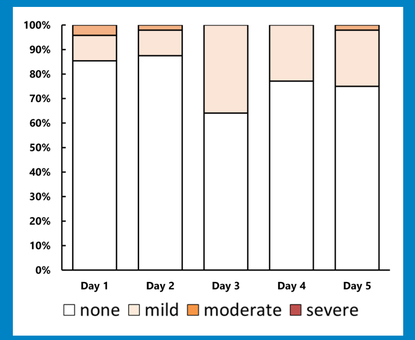


Figure 4: Decreased concentration



DISCUSSION and CONCLUSIONS

- **This study demonstrated that the administration of 15 mg of mirtazapine combined with granisetron and dexamethasone showed promising efficacy and manageable safety for the prevention of carboplatin-induced nausea and vomiting in patients with thoracic malignancies.**
- **The favorable safety profile of mirtazapine, particularly in elderly and diabetic patients, and its minimal drug-drug interactions via cytochrome P450 enzymes, make it a promising alternative to olanzapine for the prevention of chemotherapy-induced nausea and vomiting.**
- **This three-drug antiemetic regimen appears to be a reasonable treatment approach for patients with thoracic malignancies receiving carboplatin-based chemotherapy with an area under the curve (AUC) ≥ 4 mg/mL per minute.**
- **Future investigation is warranted to compare the efficacy of this mirtazapine-containing regimen to the standard triplet therapy, including an NK1 receptor antagonist, in a phase III trial.**

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