THE EFFICACY AND SAFETY PROFILE OF METHADONE FOR INTRACTABLE CANCER PAIN IN ADVANCED LUNG CANCER PATIENTS

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Abstract

- Introduction: Some patients with advanced lung cancer (LC) suffer from intractable pain, which cannot be sufficiently relieved even with strong opioid analgesics. In such cases, methadone is recommended in Japan. However, it is still unclear which patients benefit most from methadone. We aimed to explore the efficacy and safety of methadone in this population. Methods: We retrospectively reviewed patients with advanced LC who received methadone in our hospital between September 2014 and December 2022. We evaluated the number of times requiring rescue analgesics per day on the day before methadone initiation (baseline) and on the day five of methadone (D5) when the blood concentration of methadone was expected to reach a plateau. We also assessed adverse events possibly caused by methadone. Results: A total of 37 patients were included. The median age was 68 (range 42-85) years. Twenty-five patients were men. Histological types of lung cancer were adenocarcinoma (54.1%), squamous cell carcinoma (24.3%), high-grade neuroendocrine carcinoma (8.1%), and others (13.5%). The median initial dose of methadone was 20 (range 10-40) mg, and the maximum dose was 30 (range 10-80) mg. The median treatment duration was 42 (range 1-1113) days. Most patients (89.2%) had a combination of somatic and neuropathic pain. The main causes of intractable pain were vertebral metastases and invasions (64.9%), pleural dissemination and invasion (48.6%), and rib metastases and invasions (40.5%). The number of rescue doses on D5 (2.1/day) significantly decreased from the baseline (4.8/day, P <0.05). Two patients discontinued methadone due to somnolence possibly caused by methadone. Conclusion: This study indicated the favorable efficacy and safety profile of methadone for intractable cancer pain in advanced LC patients.

Introduction

- Methadone is a multi-action analgesic because of being a highly potent μ-opioid agonist and an antagonist of the N-methyl-D-aspartic acid (NMDA) receptors and inhibits the reuptake of serotonin and norepinephrine[1)2)].
- Methadone was approved in September 2012 by the Japanese regulatory authority. Since methadone is positioned as a so-called step 4 opioid in Japan[1)], it must be prescribed as an alternative opioid switched from another of 60mg/day or greater equivalent dose of oral morphine[3)].
- A proportion of patients benefit most from methadone in some patients with advanced lung cancer (LC) suffer from intractable pain, which cannot be sufficiently relieved even with strong opioid analgesics. However, it is still unclear which patients benefit most from methadone.
- We aimed to investigate the efficacy and safety of methadone in this population.

Methods

- We retrospectively reviewed patients with advanced LC who received methadone in our hospital between September 2014 and December 2022.
- We evaluated the number of times requiring rescue analgesics and a numeric rating scale (NRS) pain per day on the day before methadone initiation (baseline) and on the day five of methadone (D5) when the blood concentration of methadone was expected to reach a plateau.

Results

Patient characteristics at the start of methadone

	All patients (n = 37)
Age (years)	
Median / Range	68 / 42 - 85
Gender, n (%)	
Male	25 (67.6%)
Female	12 (32.4%)
Stage	
Advanced	37 (100%)
Histological classification, n (%)	
Adenocarcinoma	20 (54.1%)
Squamous cell carcinoma	9 (24.3%)
HGNEC	3 (8.1%)
Other	5 (13.5%)
The initial dose of methadone	
Median / Range (mg/day)	20 (10-40)
The maximum dose of methadone	
Median / Range (mg/day)	30 (10-80)
The treatment duration of methadone	
Median / Range (days)	42 (1-1113)
Combination therapy	
Other opioid analgesics, n (%)	
Yes	19 (51.4%)
Non-opioid analgesics, n (%)	
Yes	26 (70.3%)
Analgesic adjuvants, n (%)	
Yes	23 (62.2%)
Nerve blocks, n (%)	
Yes	4 (10.8%)
Palliative radiation, n (%)	
Yes	4 (10.8%)
Chemotherapy, n (%)	
Yes	16 (43.2%)

HGNEC; High-grade neuroendocrine carcinoma

Concomitant medications

Other opioid analgesic	(n)
Tapentadol	8
Tramadol	9
Morphine	2
Rescue opioids	
Oxycodone	30
Hydromorphone	5
Morphine	2

The type of pain

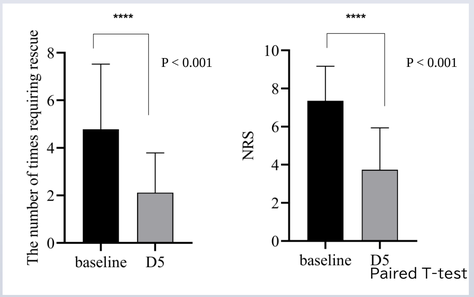
	All patients (n = 37)
Somatic and neuropathic pain	33 (89.2%)
Somatic, neuropathic, and visceral pain	2 (5.4%)
Neuropathic pain only	1 (2.7%)
Somatic pain only	1 (2.7%)

The cause of pain

	All patients (n = 37)
1) Bone metastases and invasions	30 (81.0%)
2) Pancoast tumor	9 (24.3%)
3) Pleural dissemination and invasion	8 (21.6%)
4) Muscle and soft tissue metastasis	3 (8.1%)
5) Abdominal paraaortic lymph node metastasis	2 (5.4%)
6) Visceral metastasis	1 (2.7%)

*There are some overlapping.

The efficacy of methadone



The toxicity of methadone

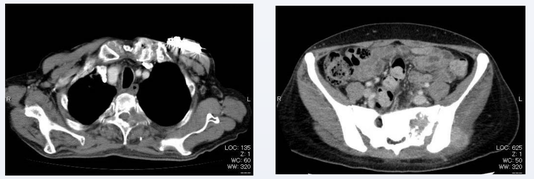
Discontinuation for toxicity	2 (5.4%)
Somnolence	1
Somnolence, myoclonus, and delirium	1

Outcome

Discontinuation due to death	28 (75.7%)
Continuing	4 (10.8%)
Discontinuation due to toxicity	2 (5.4%)
Transfer	2 (5.4%)
Other	1 (2.7%)

The typical images

Bone metastases and invasions



Pancoast tumor

Pleural dissemination and invasion

Discussion

- In this study, methadone was prescribed for intractable pain in 37 patients with advanced LC. The number of times requiring rescue analgesics and NRS score significantly decreased by methadone. Only two patients discontinued methadone due to toxicity.
- The major cause of mixed pain (somatic and neuropathic) was bone metastasis and invasion, which was common in advanced LC.
- The mixed pain by bone metastasis and invasion was often difficult to relieve, even with strong opioid analgesics. Our results suggested that combining methadone with standard analgesics was a promising strategy for alleviating intractable bone-related pain, as shown in the previous study[4)].

Conclusion

- This study indicated the favorable efficacy and safety profile of methadone-based combination analgesics for intractable cancer pain, especially bone-related pain, in patients with advanced LC.

References

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