Effects of high-dose opioid analgesia on survival, pain relief, quality of life and adverse drug reactions in cancer and neuropathic pain patients: a retrospective cohort study in real-world clinical practice

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Background: Pain is a common symptom among cancer patients and directly affects their prognosis. As the leading drug for pain management, opioids are widely prescribed. So it is necessary to get people a correct understanding and application of opioids. In order to examine whether the use of high-dose opioids might affect survival and quality of life, this retrospective cohort study was performed to explore the outcomes of patients receiving high-dose opioids for pain management in a first-class tertiary hospital in China.

Methods: We retrospectively searched medical records of inpatients and outpatients with pain who were treated with opioids in The First Affiliated Hospital, Zhejiang University School of Medicine from July to December 2021. Forty-three cases who were treated with high-dose opioids meeting inclusion criteria. Among these patients, 37 had cancer pain and 6 had neuropathic pain. All patients had regular follow-up when readmission until to April 7, 2022. Medical records of patients on high-dose opioids (equivalent to morphine ≥300 mg/d) was collected, including numerical rating scale (NRS), Karnofsky performance score (KPS), survival and adverse drug reactions (ADRs). Pain relief, quality of life, survival, and ADRs of patients after pain treatment were analyzed and evaluated.

Results: The NRS score was significantly reduced and pain was relieved after high-dose opioid treatment. The before and after average NRS score of cancer pain was 5.2±1.6 *vs.* 2.2±1.1 points (P<0.001), neuropathic pain was 5.0±2.2 *vs.* 1.3±1.2 points (P<0.05), respectively. Although there is no statistical difference, quality of life showed a trend of improvement compared with before treatment. The before and after average KPS scores of cancer pain patients was 55.7±17.3 *vs.* 62.4±20.0, and neuropathic pain patients was 71.7±9.0 *vs.* 83.3±4.7. There were no intolerable ADRs. The median survival time was 238 days and 83 days in patients with cancer pain who received high-dose opioids and ultra-high dose opioids (equivalent to morphine ≥600 mg/d).

Conclusions: Multimodal high-dose opioid pain treatments are important approaches to effectively relieve moderate to severe pain and improve the quality of life of patients. This study provides a clinical basis for future pain treatment with high-dose opioids.

Keywords: High-dose opioids; pain; efficacy; survival; quality of life

Submitted Jul 13, 2022. Accepted for publication Sep 13, 2022.
doi: 10.21037/atm-22-4242
View this article at: https://dx.doi.org/10.21037/atm-22-4242

Introduction

Pain is the most common symptom of many clinical diseases. Pain not only brings physical discomfort to patients, but also causes psychological stress and emotional disturbance, which increases the occurrence of complications. It is extremely important to manage pain. Up to 2020, the number of patients with chronic pain has exceeded 300 million, and is still growing rapidly at a rate of 10 to 20 million per year in China (1,2). Opioids are pivotal drugs for the treatment of moderate to severe pain. With the increasing incidence of pain, the use of opioids has also increased accordingly. However, because of their addictive properties, there are many limitations to their clinical application (3,4). In order to ensure the rational and safe use of high-dose opioids, Zhejiang Province advocates a policy package to standardize the treatment of cancer pain, such as building a model ward for the standardized treatment of cancer pain. Only after consultation and agreement of the hospital's expert group for standardized treatment of cancer pain, the pharmacy department can adjust and distribute drugs.

Several studies have reported that high-dose opioids can quickly and effectively relieve intermediate or severe pain without intolerable adverse reactions (5,6). However, there are few clinical studies on the survival of patients using high-dose opioids from China. Although opioids have beneficial effects, they also have a range of adverse effects. These include constipation, emesis, cognitive dysfunction, and addiction, and also more recent concerns about effects on immune function, cancer growth, and even their impact on survival. Considering that high-dose opioids may lead to increased risk of adverse reactions for clinicians, patients, and carers, the rational use of high-dose opioids by WHO recommendation was limited (7). On one side, high-dose opioids could potentially affect survival by having acute or chronic effects. On the other side, high-dose opioids could potentially be associated with a longer survival because of improvements in pain, as higher pain scores in patients with cancer are associated with a shorter survival. However, the overall effect of high-dose opioids on these outcomes in clinical practice is poorly understood (8). Aiming to enable people to have a correct understanding and rational application of opioids, it is necessary to carry out comprehensive evaluation about the efficacy of high-dose opioids in the treatment of moderate to severe cancer pain.

In this study, we retrospectively analyzed the use of opioids, pain relief, quality of life, survival, and adverse reactions to high-dose opioids analgesics. These results may provide clinical evidence for the use of high-dose opioids in the treatment of pain. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4242/rc).

Methods

Case data

This study was a retrospective cohort study in real-world clinical practice. This study was conducted in a first-class tertiary hospital, The First Affiliated Hospital, Zhejiang University School of Medicine, for the treatment of pain cases. All cases used high-dose opioids to treat pain during the outpatient or inpatient period. From July to December 2021, a total of 43 patients were admitted. All those patients had regular follow-up when readmission until to April 7, 2022. The types of high-dose opioids included oxycodone prolonged-release tablets, fentanyl transdermal patches, hydromorphone injection, and morphine injection. Referring to relevant literature (3), high-dose opioid analgesia was defined as oral morphine equivalent ≥300 mg/d. And ultra-high dose opioid analgesia was defined as oral morphine equivalent ≥600 mg/d. Other opioid dose conversions refer to "Cancer Pain Diagnosis and Treatment Standards (2018 Edition)" (9).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the clinical research ethics committee of The First Affiliated Hospital, Zhejiang University School of Medicine (No. IIT20220565A). All cases were recruited retrospectively, therefore individual informed consent was not required by the ethics committee.

Outcomes

The use of high-dose opioids and the pain relief, quality of life, survival time, and adverse drug reactions (ADRs) of patients taking high-dose opioids for analgesia were statistically analyzed.

Pain scale

The numerical rating scale (NRS) score was used to evaluate the pain relief of patients: 0 was no pain, 1–3 was mild pain, 4–6 was moderate pain, and 7–10 was severe pain. Pain Relief (PAR) = (NRS score before medication – NRS score after medication)/NRS score before medication ×100%. PAR <25% means no relief, PAR =25–49% means mild relief, PAR =50–74% means moderate relief, PAR =75–99% means significant relief, and PAR =100% means complete relief. The total effective rate of pain treatment was the rate of moderate relief + significant relief + complete relief.

Quality of life

Before treatment and 4 weeks after treatment, the Karnofsky performance score (KPS) was used to measure the patient's overall performance status or ability to perform their activities of daily living. KPS is a single score between 10 and 100, and a higher score signifies better functional status of patients.

Survival

The time from the initiation of high-dose opioids for pain treatment to the death of the patient was recorded during follow-up. And the observational period was set till April 7, 2022.

Opioid treatment outcomes

Follow-up records of patients' opioid dose maintenance, reduction, increase, or withdrawal were obtained.

Adverse drug reactions

The occurrence of ADRs such as nausea, vomiting, constipation, dysuria, and psychiatric symptoms after taking opioids was recorded during follow-up.

Statistical analysis

All analyses were performed using Statistical Package for the Social Sciences (SSPS, 25.0 version). Quantitative data (continuous variables) were shown as mean ± standard deviation. Within- and between-group variables were analyzed using a *t*-test. Qualitative data (categorical variables) were expressed as the number of cases and rate (%). Survival curves were drawn by Prism 9.0, and log-rank test analysis was performed to analyze the survival of different groups. The significance level was set at $P<0.05$ (two-side test).

Results

Characteristics of patients

July to December 2021, 43 patients were referred to us for inclusion. Among them, there were 27 males and 16 females, aged 54.7±13.16 years. The types of pain were cancer pain in 37 cases (86%) and neuropathic pain in 6 cases (14%). Ten subjects received oxycodone sustained-release tablets, 15 cases received fentanyl transdermal patches, 16 cases received hydromorphone injection, and 2 cases received morphine injection. A total of 23 cases received the morphine equivalent of 300–599 mg/d (high dose) and 20 cases received ≥600 mg/d (ultra-high dose, *Figure 1A*). Among the 23 patients who received high-dose opioids, 8 received oxycodone prolonged-release tablets, 9 received fentanyl transdermal patches, and 6 received hydromorphone injection. In the ultra-high dose subgroup, fentanyl transdermal patches were used in 6 cases, hydromorphone injection was used in 10 cases, and morphine injection was used in 2 cases (*Figure 1B*). The routes of administration included oral administration in 10 cases, transdermal patches in 15 cases, and patient controlled analgesia (PCA) in 18 cases (including 8 cases of intravenous PCA and 10 cases of intrathecal PCA). The general information of the patients, such as KPS score, NRS score, disease diagnosis, opioids, route of administration, and combined analgesic drugs before treatment, is shown in *Table 1*.

Pain relief

Before treatment with high-dose opioids, 30.2% of the patients had mild pain (NRS ≤3 points) and 69.8% of the patients had moderate to severe pain (NRS ≥4 points) among the 43 patients (*Table 1*). The average NRS score of the 37 patients with cancer pain was 5.2±1.6 points, the average NRS score of the 6 patients with neuropathic pain was 5.0±2.2 points, and after treatment, the mean NRS scores of the two groups decreased to 2.2±1.1 and 1.3±1.2 points, respectively. A total of 93% of all patients

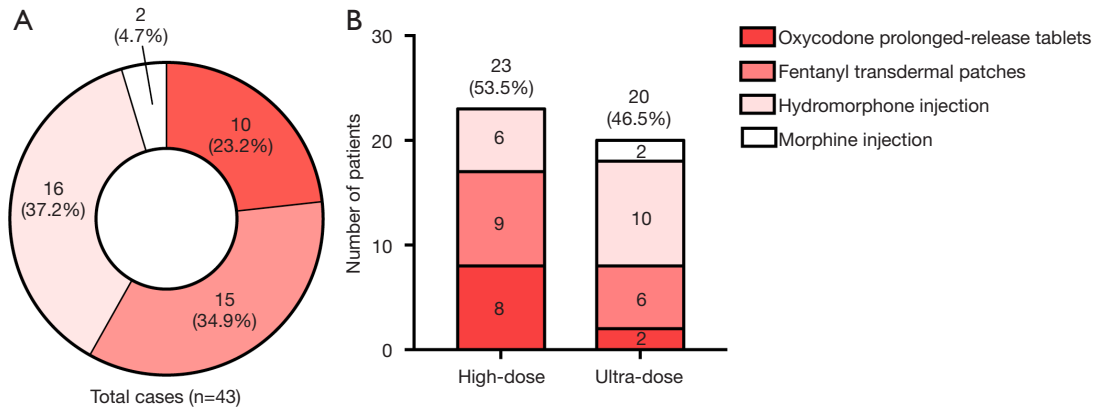

Figure 1 The situation of high-dose opioids used in this study. (A) Type of opioids used in 43 patients; (B) type of opioids used in 2 subgroups, high-dose and ultra-high dose.

had mild pain, which was significantly relieved compared with before treatment (P<0.001, P<0.05), indicating that high-dose opioids had a significant analgesic effect (*Table 2*). In patients with cancer pain, the number of cases that had moderate pain relief was 21, 7 had significant relief, and 2 had complete relief. The complete relief rate of high-dose opioids in the treatment of cancer pain was 5.4%, and the effective relief rate was 81.1% (*Table 3*). In patients with neuropathic pain, 2 cases had moderate relief, 1 case had significant relief, and 2 cases had complete relief. The complete relief rate of high-dose opioids in the treatment of neuropathic pain was 33.3%, and the effective relief rate was 83.3% (*Table 3*).

Quality of life

At baseline, the average KPS scores of cancer pain and neuropathic pain patients were 55.7±17.3 and 71.7±9.0, respectively. After high-dose opioid treatment, the KPS scores of cancer pain and neuropathic pain patients increased to 62.4±20.0 and 83.3±4.7, respectively, suggesting that the patients' physical fitness and quality of life improved, but there was no significant difference (*Table 4*).

Survival

According to different types of pain, 43 patients with pain were divided into the cancer pain group (37 cases) and neuropathic pain group (6 cases). The survival time of patients was statistically analyzed (*Table 5*). By the end of follow-up on April 7, 2022, among the 37 patients in the cancer pain group, 21 cases died while 16 were still alive or lost to follow-up. The median survival time was 238 days (95% CI: 221.6, 256.4, *Figure 2*). The median survival time of cancer pain patients who died was 75 days (95% CI: 94.1, 53.1, *Figure 3*). Six patients in the neuropathic pain group still survived at the end of the observation period. Furthermore, different dosages of opioids in patients with cancer pain suggested that there were differences in the degree of malignancy. We divided all patients with cancer pain into 2 subgroups, namely the high-dose group (equivalent to morphine 300–599 mg/d, 19 cases) and the ultra-high dose group (equivalent to morphine ≥600 mg/d, 18 cases). At the end of follow-up, 8 patients in the high-dose group died, 11 patients were still alive or lost to follow-up, and the median survival time was not determined. Thirteen patients died in the ultra-high dose group, 5 patients were still alive or lost to follow-up at the end of the observation period, and the median survival time was 83 days (95% CI: 62.1, 107.5, *Table 6*, *Figure 4*).

Opioid treatment outcomes

The clinical outcomes of opioid treatment mainly included dose maintenance, increase, decrease, without use due to disease remission, and without use due to death. By the end of follow-up on April 7, 2022, among the 43 patients, 6 patients were on a maintenance dose, 3 patients were dose-increased, 5 patients were dose-decreased, 2 patients had withdrawal due to disease remission, 21 patients did not use due to death, and 6 patients were lost follow-up (*Table 7*).

Table 1 Clinical characteristics of patients using high-dose opioids

Patient characteristics	n (%)
Age (years), mean ± SD	54.7±13.16
Sex	
Male	27 (62.8)
Female	16 (37.2)
KPS (before treatment)	
≤30	5 (11.6)
40–60	18 (41.9)
≥70	20 (46.5)
NRS (before treatment)	
Mild pain [0–3]	13 (30.2)
Moderate pain [4–6]	15 (34.9)
Severe pain [7–10]	15 (34.9)
Types of pain	
Cancer pain	37 (86.0)
Neuropathic pain	6 (14.0)
Pain sites	
Chest	6 (14.0)
Low back	5 (11.6)
Abdomen	10 (23.3)
Shoulder and neck	1 (2.3)
Limbs	3 (7.0)
Other	5 (11.6)
Combined pain in multiple places	13 (30.2)
Daily morphine equivalent	
High-dose (300–599 mg/d)	23 (53.5)
Ultra-high dose (≥600 mg/d)	20 (46.5)
High-dose opioids	
Oxycodone prolonged-release tablet	10 (23.2)
Fentanyl transdermal patch	15 (34.9)
Hydromorphone injection	16 (37.2)
Morphine injection	2 (4.7)
Routes of administration	
Oral	10 (23.3)
Transdermal patch	15 (34.9)
Intravenous PCA	8 (18.6)
Intrathecal PCA	10 (23.3)
Disease diagnosis	
Lung cancer	6 (14.0)
Pancreatic cancer	6 (14.0)
Malignant tumors of the stomach and duodenum	2 (4.7)
Hepatic carcinoma	4 (9.3)
Colorectal cancer	7 (16.3)
Cervical malignant tumors	2 (4.7)
Neuroendocrine neoplasm	2 (4.7)
Other cancers	8 (18.6)
Neuropathic pain	6 (14.0)
Combined analgesics	
NSAIDs	14 (32.6)
Celecoxib	6 (14.0)
Flurbiprofen	4 (9.3)
Indomethacin	2 (4.7)
Propacetamol	1 (2.3)
Etoricoxib	3 (7.0)
Anticonvulsant drugs	22 (51.2)
Gabapentin	3 (7.0)
Pregabalin	20 (46.5)
Anti-depressants	2 (4.7)
Not used	17 (39.6)

KPS, Karnofsky performance score; NRS, numerical rating scale; PCA, patient controlled analgesia; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 Comparison of NRS scores before and after high-dose opioid treatment ($\bar{x} \pm s$)

Groups	n	Before treatment	After treatment
Cancer pain	37	5.2±1.6	2.2±1.1[a]
Neuropathic pain	6	5.0±2.2	1.3±1.2[b]

[a], P<0.001; [b], P<0.05. NRS, numerical rating scale.

Table 3 Pain relief rate after high-dose opioid treatment [n (%)]

Groups	n	No relief	Mild relief	Moderate relief	Significant relief	Complete relief	Effective relief
Cancer pain	37	3 (8.1)	4 (10.8)	21 (56.8)	7 (19.0)	2 (5.4)	81.1%
Neuropathic pain	6	0 (0.0)	1 (16.7)	2 (33.3)	1 (16.7)	2 (33.3)	83.3%

Table 4 Comparison of KPS scores before and after high-dose opioid treatment ($\bar{x} \pm s$)

Groups	n	Before treatment	After treatment
Cancer pain	37	55.7±17.3	62.4±20.0
Neuropathic pain	6	71.7±9.0	83.3±4.7

KPS, Karnofsky performance score.

Table 5 Survival of cancer pain patients treated with high-dose opioids

Groups	n	Censored data	Median survival (day)	95% CI (day)
Cancer pain	37	16	238.0	221.6–256.4
Neuropathic pain	6	6	Undefined	–

CI, confidence interval.

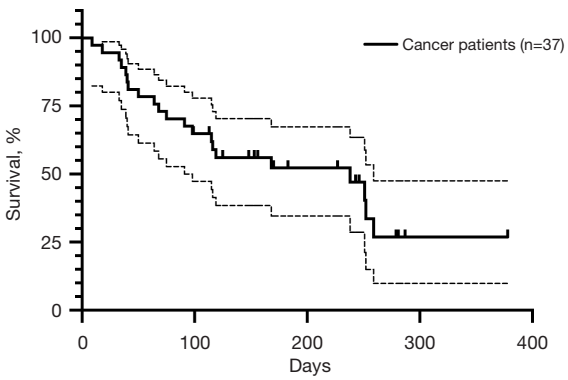

Figure 2 Survival of all cancer patients with pain. The dotted lines are lower and upper limits of 95% CI. CI, confidence interval.

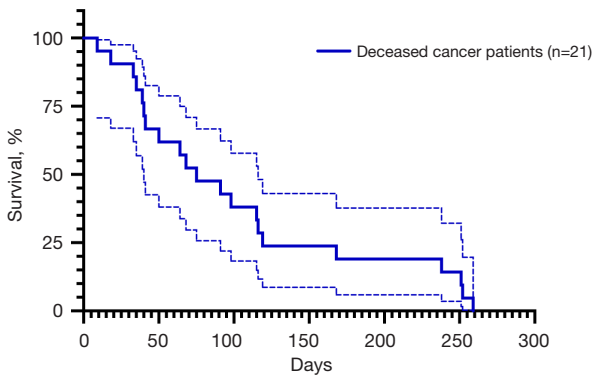

Figure 3 Survival of deceased cancer pain patients (n=21). The dotted lines are lower and upper limits of 95% CI. CI, confidence interval.

Table 6 Survival of cancer patients with pain on different dosages of opioids

Treatment modality	n	Censored data	Median survival (day)	95% CI (day)
High-dose (300–599 mg/d)	19	11	Undefined	–
Ultra-high dose (≥600 mg/d)	18	5	83	62.1–107.5

CI, confidence interval.

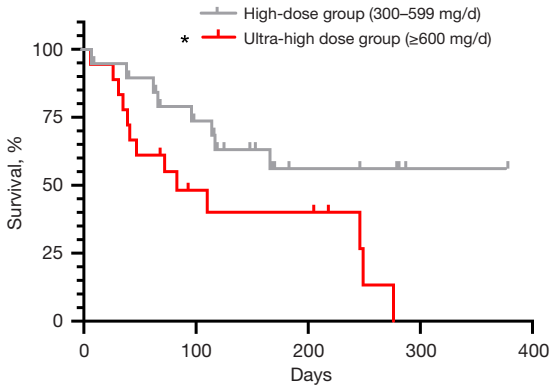

Figure 4 Survival of cancer pain patients treated with ultra-high dose opioids. *, P<0.05.

Table 7 Outcomes of opioids in the treatment of cancer patients with pain

Outcomes	n (%)
Dose maintenance	6 (14.0)
Dose increase	3 (7.0)
Dose decrease	5 (11.6)
Withdrawal due to disease remission	2 (4.7)
Death	21 (48.8)
Loss to follow-up	6 (14.0)

Table 8 ADRs of opioids

ADRs	n (%)
Nausea	16 (37.2)
Vomiting	12 (28.0)
Constipation	12 (28.0)
Dysuria	3 (7.0)
Psychiatric symptoms	8 (18.6)

ADRs, adverse drug reactions.

ADRs

The main ADRs in the 43 patients included nausea, vomiting, constipation, dysuria, and psychiatric symptoms. The highest incidence was nausea, with 16 cases, accounting for 37.2%. In second place was vomiting, with 12 cases, accounting for 28% (*Table 8*). All ADRs were treated symptomatically with corresponding measures, and some were significantly relieved after treatment.

Discussion

Pain is a common, complex, and distressing problem, which has a significant impact on society and individuals. Disease progression often leads to aggravation of pain, which severely affects patients' physical and mental health. Effective treatment of pain can not only alleviate the suffering of patients, but also improve their quality of life. Opioids are the main drugs for the treatment of moderate to severe pain, and have been listed by the World Health Organization as the first-line therapy for relieving cancer pain (10). As the number of cancer patients is rising with each year (11), the use of opioids in patients with chronic non-cancer pain increases (12), along with changes in public attitudes of opioids in pain management (13), and the consumption rates of opioids have increased accordingly. Although opioids have no ceiling effect in the treatment of cancer pain, the dose can be determined according to the patient's condition and tolerance (9), but due to their addictive nature, there are still many restrictions in clinical application. In particular, clinical studies are still lacking with regard to the survival of patients who use high-dose opioids.

This study retrospectively analyzed 43 patients in our hospital who were treated with high-dose opioids for pain, including 37 patients with cancer pain and 6 patients with neuropathic pain. The types of drugs were oxycodone prolonged-release tablets, fentanyl transdermal patches, hydromorphone injection, and morphine injection. Routes of administration included oral, transdermal patches, intravenous PCA, and intrathecal PCA. Oxycodone prolonged-release tablets and fentanyl transdermal patches are μ-opioid receptor complete agonists with high bioavailability. Both are recommended drugs for the treatment of moderate to severe cancer pain and chronic non-cancer pain by "Cancer Pain Diagnosis and Treatment Standards (2018 Edition)" in China, the American National Comprehensive Cancer Network (NCCN) guidelines, and the European Pain Federation (EFIC) (9,14). PCA technology can be used for patients with refractory pain who cannot effectively relieve pain or have intolerable ADRs after standardized treatment due to disease progression (15). The preferred opioids for PCA include morphine injection and hydromorphone injections, fentanyl injections. Multimodal opioid analgesia enables patients to obtain more optimized analgesia and quality of life. The results

of this study showed that the mean NRS scores of the 37 patients with cancer pain and 6 patients with neuropathic pain were significantly decreased after treatment with high-dose opioids, and the proportion of patients with moderate to severe pain decreased from 69.8% to 7%. The pain symptoms were significantly relieved, both in the high-dose and ultra-high dose opioids subgroups ($P<0.001$, $P<0.05$), and the effective remission rate of patients in each dose group was over 80%. At the same time, after treatment with high-dose opioids, the KPS scores of 43 patients also increased, although there was no significant difference. These findings suggest that high-dose opioids may improve patients' quality of life. The results of our study are basically consistent with other reports. High-dose opioids have a good analgesic effect in the treatment of moderate to severe pain (5,16) and significantly improve patients' daily state (17), and the multimodal route of administration facilitates efficient analgesia (18).

Importantly, this study statistically analyzed the survival time of patients using high-dose opioids, and the median survival time of the 37 patients with cancer pain was 238 days. This finding is different from early reports. Two independent analyses of the survival of cancer pain patients treated with opioids for palliative care showed that the median survival time was only about 40 days (19). Another retrospective study showed a shorter median survival time of 16 days (20). The above-mentioned studies did not limit the dosage of opioids, and the conditions for the inclusion of patients were the palliative care population. Due to the relatively limited number of patients needing high-dose opioid analgesia in this study, the sample size was small, and the proportion of censored cases lost to follow-up was large, which makes the statistical analysis results of median survival time different from previous studies to a certain extent. We also separately calculated that the survival time of dead cancer pain patients was 75 days, which is basically consistent with other reports. These results provide clinical evidence for the use of high-dose opioids in our hospital. It is noteworthy that all 6 patients with neuropathic pain survived until the end of the observation period, suggesting that the primary disease causing pain may be an important factor affecting survival time.

In this study, 37 patients with cancer pain were also divided into the high-dose group (300–599 mg/d) and ultra-high dose group (≥600 mg/d), according to the daily morphine equivalent of opioids used. The median survival time in the ultra-high dose group was 83 days. The survival curve shows that cancer pain patients treated with ultra-high dose opioids had poor prognosis, and the median survival time was significantly shorter than that in the high-dose group ($P<0.05$). However, the results of our study are inconsistent with previous studies. Bercovitch and Adunsky (6) and Portenoy *et al.* (21) retrospectively analyzed the effect of high-dose morphine (≥300 mg/d) on the survival time of patients with advanced cancer pain. There was no difference in survival for patients with lower doses of morphine. These reports are all based on the comparison of high-dose and low-dose morphine. Our study paid more attention to the difference in the effect of ultra-high dose and high-dose morphine on survival time. Cancer pain patients treated with ultra-high dose opioids have more severe primary disease, therefore, the survival time is relatively shorter, which is basically in line with clinical practice.

Increase in the dose of opioids may result in increased ADRs, including nausea, vomiting, constipation, dizziness, drowsiness, dysuria, and respiratory depression. In this study, high-dose opioids were well tolerated, and no patients discontinued due to adverse effects. The ADR with the highest incidence was nausea, followed by vomiting and constipation. In clinical practice, patients are informed of the possible ADRs of opioids, and most can be alleviated by taking appropriate measures. A clinical study in Israel reported the occurrence of ADRs in 97 patients with cancer pain after treatment with high-dose oxycodone, and results showed that the incidence was comparable to that of the middle and low-dose groups (6). Bercovitch and Adunsky's study also confirmed that high-dose opioids have a wide range of clinical safety applications (3).

In conclusion, we retrospectively analyzed the survival states of patients with pain who received high-dose opioids, including pain relief, quality of life, survival time, and ADRs. It is suggested that multimodal high-dose opioid for pain treatment is important for effectively relieving moderate to severe pain and improving the quality of life of patients with pain, without intolerable ADRs. The median survival time of cancer pain patients receiving high-dose opioid analgesia (equivalent to morphine ≥300 mg/d) was 238 days, while the prognosis of cancer pain patients receiving ultra-high dose analgesia (≥600 mg/d) was poor, and the median survival time was 83 days, significantly shorter than that of patients with cancer pain on a daily morphine equivalent dose <600 mg. These results can provide a clinical basis for pain treatment with high-dose opioids in the future, but the small sample size may affect the reliability of the conclusions of this study. Since the

clinical need for high-dose opioid analgesia is relatively limited in patients, it is necessary to design a large-sample prospective multicenter study to further confirm the results of this study.

Acknowledgments

The authors appreciate the academic support from the AME Pain Management Collaborative Group.
Funding: This study was supported by Medical health science and technology project of Zhejiang provincial health commission (No. 2020KY1036) and Zhejiang pharmaceutical association hospital pharmaceutic research project (No. 2019ZYYG02).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4242/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4242/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4242/coif). MS reports that he received collaborative and non-collaborative research funding from Shionogi & Co., Ltd., Nippon Zoki Pharmaceticals, Heartfelt Inc., Nipro, and Eisai Co., Ltd; payments for his educational presentations from Daiichi Sankyo Inc. and GSK plc. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the clinical research ethics committee of The First Affiliated Hospital, Zhejiang University School of Medicine (No. IIT20220565A). All cases were recruited retrospectively, therefore individual informed consent was not required by the ethics committee.

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(English Language Editor: C. Betlazar-Maseh)

Cite this article as: Hao X, Zhou Y, Ling Y, Miyoshi H, Sumitani M, Chan KY, Park HJ, Feng Z, Rao Y. Effects of high-dose opioid analgesia on survival, pain relief, quality of life and adverse drug reactions in cancer and neuropathic pain patients: a retrospective cohort study in real-world clinical practice. Ann Transl Med 2022;10(18):998. doi: 10.21037/atm-22-4242

