Original Article



# Impact of individualized pharmaceutical care on efficacy and safety of opioid-tolerant outpatients with cancer pain: a multicenter randomized controlled trial

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**Background:** Managing cancer pain is a growing challenge. Individualized pharmaceutical care is particularly important for opioid-tolerant outpatients due to variation in terms of their knowledge about pain, treatment adherence, and risk of experiencing inadequate analgesia and severe adverse events. This study aimed to determine the influence of individualized pharmaceutical care on outcomes in opioid-tolerant outpatients with cancer pain.

**Methods:** A multicenter, open-label, randomized, controlled study was carried out. Opioid-tolerant outpatients experiencing chronic cancer pain and receiving sustained-release opioids were randomly assigned to the intervention group and the control group with a 1:1 ratio. The intervention group received individualized pharmaceutical care, while the control group received conventional care during 4-week period.

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The primary endpoint was medication adherence on the intention-to-treat (ITT) population. Secondary outcomes included the patients' knowledge of cancer pain and pain medications, pain score, frequency of breakthrough pain, quality of life (QoL) which were assessed on the ITT population. Adverse events were evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE) version 4.0 on the per-protocol (PP) population.

**Results:** A total of 118 patients were enrolled, and 102 patients (51 in each group) completed the 30-day follow-up from six oncology centers in China. The proportion of patients adhering to opioid medication increased to similar levels in the two groups during the 4 weeks (P=0.149). The intervention group had a significantly lower pain score at 4 weeks compared to the control group (P=0.015), and the proportion of participants without breakthrough pain was significantly higher at 4 weeks than at baseline in the intervention group (P=0.029), but not in the control group (P=0.322). The two groups did not differ significantly in terms of QoL or adverse events.

**Conclusions:** Our results suggest that individualized pharmaceutical care can markedly reduce patient-related problems and significantly improve pain control in opioid-tolerant outpatients. These findings validate the recommendations to include clinical pharmacists in the management of cancer pain.

**Trial Registration:** ClinicalTrials.gov identifier: NCT03439904.

**Keywords:** Cancer pain; pharmacists; pharmaceutical service; opioids; outpatients

Submitted Aug 05, 2022. Accepted for publication Sep 06, 2022.
doi: 10.21037/atm-22-4091
**View this article at:** https://dx.doi.org/10.21037/atm-22-4091

## Introduction

Pain is one of the most distressing problems that compromise the quality of life (QoL) of cancer patients and their treatment outcomes (1,2). A substantial proportion of cancer patients (30–50%) report moderate to severe pain (3,4), and 40–55% of them consider their pain management to be inadequate (5-9). Opioid requirement and chronic pain are independent predictors of survival (10-15), and severe pain is associated with shorter survival, with mean hazard ratios ranging from 1.04 to 1.39 (10,12,14,15). Pharmacists can improve the management of cancer pain through interventions such as medication reviews, patient education, the detection and management of adverse drug reactions, and pain assessments (16-20), which are well accepted by physicians in the United States (US) and Canada (16).

The perception of inadequate pain control among patients can arise due to the application of inappropriate methods to assess pain, insufficient knowledge of cancer pain treatments, anxiety, depression, and non-adherence to analgesic regimens (21-24). Human genetic variations, such as μ-opioid receptor 1 (*OPRM1*), *CYP2D6*, and catechol-O-methyl transferase (*COMT*), might be major contributors to the unpredictable clinical responses to opioids (25). These multifaceted barriers highlight the need for multidisciplinary intervention during pain management.

Pharmacists can play an important role in such multidisciplinary approaches and have a positive impact on pain control and QoL in cancer pain patients (19,26-30). However, there are few randomized controlled studies investigating the effect of pharmacist intervention on patients with cancer pain. A multicenter randomized controlled study in Guangzhou China demonstrated that pharmacist-led medication education could result in improved pain control in patients with cancer. Nonetheless, this study only analyzed the impact of medication education provided by pharmacists (28). And other previous studies also have focused on only one or a few of the areas where pharmacists can contribute to cancer pain management, such as patient education, optimization of analgesic prescriptions, and monitoring of adverse drug reactions (16-20,26-30). However, clinical practice requires that pharmacists continuously engage in all of these activities in a way that takes into account each patient individually. Moreover, previous studies did not pay attention to the needs of specific cancer pain patients such as opioid-tolerant patients and outpatients for individualized services. In practice, individualized care is particularly important for

 

opioid-tolerant patients (those receiving at least 60 mg of morphine daily or an equianalgesic dose of another opioid for ≥1 week), who demonstrate greater variation than opioid-naïve patients in terms of their knowledge about pain, their treatment adherence, and their risk of experiencing inadequate analgesia and severe adverse events (31-33). More generally, individualized care is particularly important for outpatients who are not under constant medical supervision and may therefore be more likely to deviate from the recommended treatment (34).

Herein, we performed a prospective, randomized controlled study at six major oncology centers across China to evaluate the impact of individualized pharmaceutical care on outcomes related to cancer pain in opioid-tolerant outpatients. We focused on medication adherence, analgesic efficacy, QoL, and adverse events. We present the following article in accordance with the CONSORT reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4091/rc).

## Methods

### *Study design and participants*

A multi-center, open-label, randomized controlled trial was performed at six Chinese oncology centers. The study was conducted according to the Good Clinical Practice guidelines and the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethical committees of each participating center (Table S1). All patients provided written informed consent.

The following inclusion criteria were used: opioid-tolerant patients with chronic cancer pain (pain that has lasted for ≥3 months) who were treated with sustained-release opioids [at least 25 mcg/h of fentanyl patch, 60 mg of morphine daily, or 30 mg of oral oxycodone daily (35)] were prospectively enrolled if they were at least 18 years old, their Karnofsky performance status score was ≥50, and their estimated survival was at least 3 months.

Patients were excluded if they presented any of the following: treatment with patient-controlled analgesia, creatinine clearance rate <15 mL/min, alanine transaminase or aspartate aminotransferase >10-fold the upper normal limit (36), pathological fracture, intestinal obstruction, severe infection, intractable constipation unrelated to opioids, cognitive impairment, or mental disorder.

Patients were removed from the study if they did not tolerate opioid therapy or were switched to non-sustained-release opioids.

### *Randomization and interventions*

Patients were randomly assigned (1:1 ratio) to receive either pharmacist intervention or conventional care on an outpatient basis. Randomization was performed by Tong YH (Zhejiang Cancer Hospital) using the permuted block randomization method. The allocation was concealed using the sealed opaque envelopes. The intervention group received individualized pharmaceutical care based on a comprehensive assessment at baseline and during follow-up (*Figure 1*).

The first intervention was a face-to-face baseline assessment of the patients' knowledge about cancer pain and medication (Figure S1), medication adherence (37), and appropriateness of the analgesic scheme (Table S2). Educational materials on cancer pain management were also provided at the first intervention, which covered pain assessment methods, principles of cancer pain treatment, precautions when using analgesics, as well as the prevention and treatment of opioid-related adverse reactions. Subsequent interventions were conducted once a week by telephone over a 4-week period, with a second assessment conducted at the end of week 4. The follow-up period was set at 4 weeks to investigate whether pharmacist intervention could improve pain management in the short term. The conventional care included a telephone follow-up provided by a nurse within 1 week after the clinic visit and concise medication instructions along with drug dispensing in the outpatient pharmacy.

The control group underwent a similar baseline assessment, but they received conventional care without individualized pharmacist interventions during the remainder of the 4-week period (*Figure 1*).

### *Primary and secondary outcomes*

The primary outcome was medication adherence in the per-protocol (PP) population. Secondary outcomes included the patients' knowledge of cancer pain and medications, pain score, frequency of breakthrough pain, QoL, and adverse events.

The patients' medication adherence, pain score, QoL, and knowledge of cancer pain and analgesics were assessed by a face-to-face interview in the hospital on the first day and telephone intervention on day 30±1. Adverse events related to pain treatment were collected on days 1, 8±1,

 

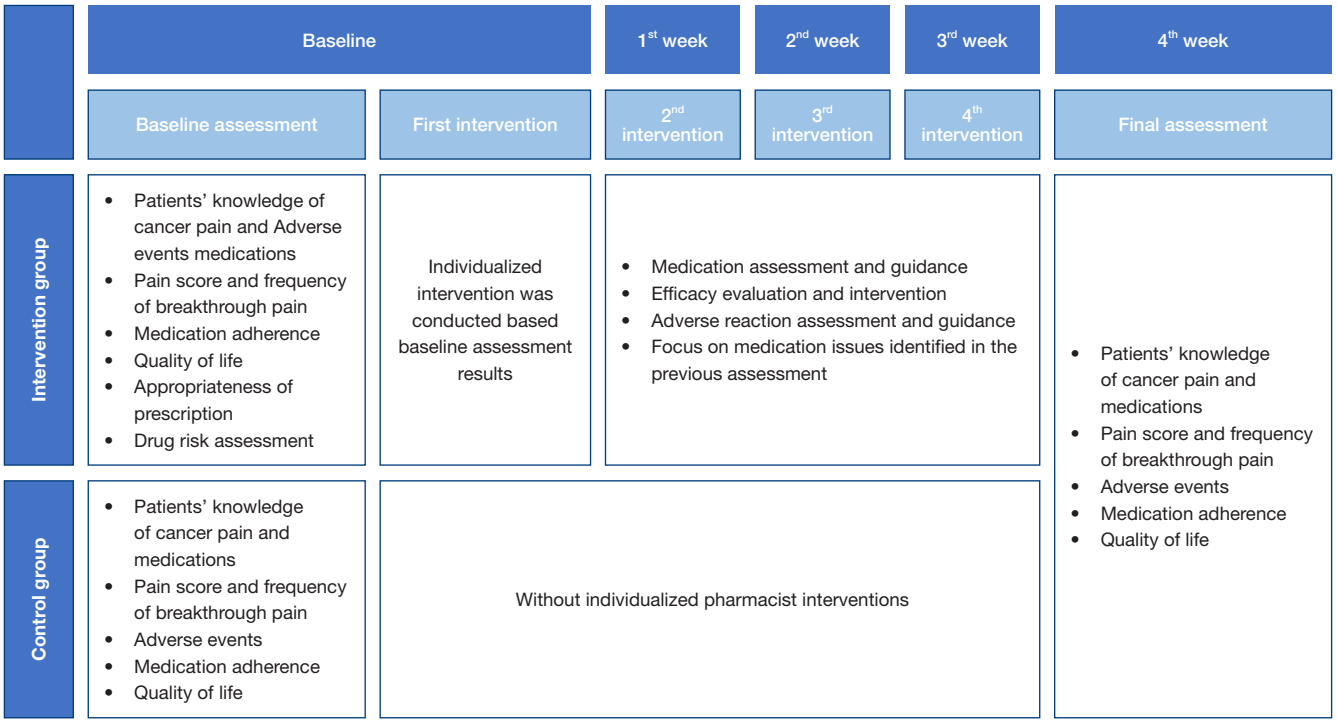


**Figure 1** Scheme of the individualized intervention provided by pharmacists to the intervention group.

15±1, 23±1, and 30±1.

### *Medication adherence*

Pain medication adherence was assessed using the self-reported medication adherence scale (37,38). Total score ranges from 0 to 4: 0–1= low adherence; 2–3= moderate adherence; 4= high adherence.

### *Knowledge about cancer pain and analgesics*

The patients' knowledge about cancer pain and medications was evaluated using a custom-designed questionnaire of 16 items involving knowledge about cancer pain, including its treatment and medications (Figure S1). Higher scores indicated better knowledge.

### *Pain score and breakthrough pain*

Pain score during the last 24 hours was assessed using a numeric rating scale involving patients' self-reports on the intensity of their pain as a number usually ranging from 0 to 10, where "0" represents "no pain" and "10" denotes pain as "bad as it could be" (39). The frequency of breakthrough pain during the last 7 days was also recorded.

### *QoL*

QoL of patients was assessed using EuroQol-5 Dimension 3-Level (EQ-5D-3L) (40), which covers five domains: mobility, self-care, usual activity, pain, and anxiety/depression.

### *Safety and tolerability*

Adverse events related to pain treatment and analgesics were assessed according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE, version 4.0) (41).

### *Statistical analysis*

Assuming that the rate of high adherence to pain treatment at week 4 would be 15% higher in the intervention group than in the control group, we calculated that a sample of 118 patients would provide a power of 80% at a significance level (alpha) of 0.05, based on a two-sided, two-sample *t*-test.

Binary outcomes were reported as frequencies and

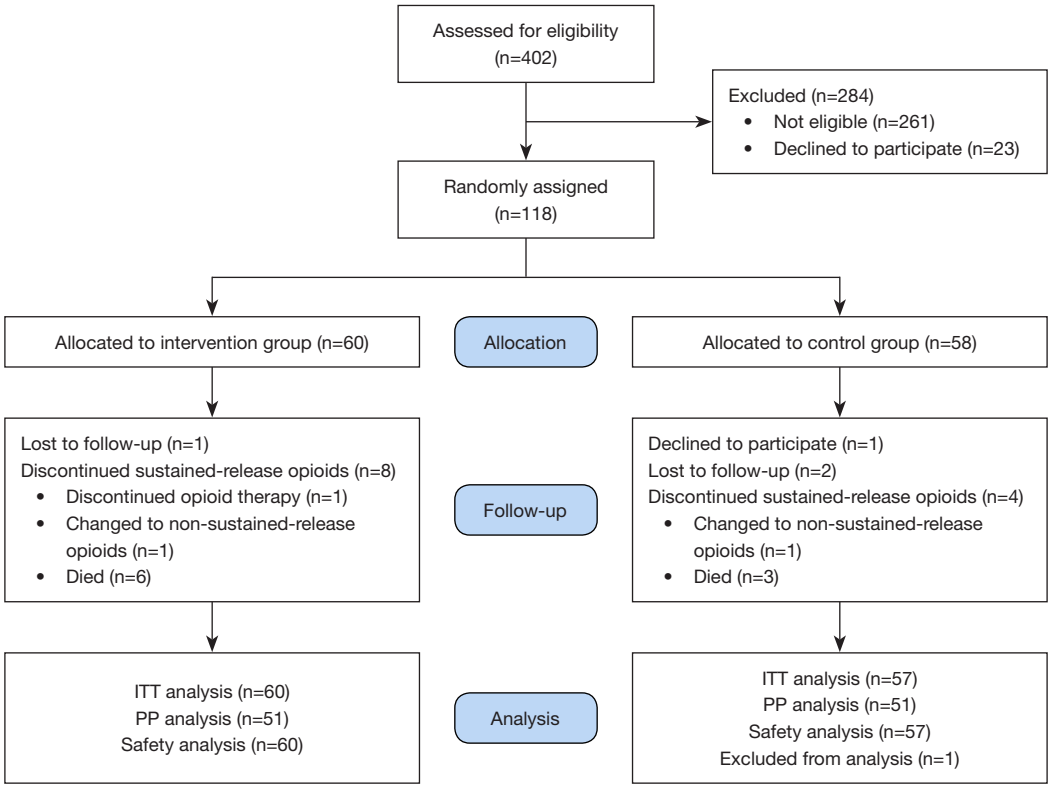


**Figure 2** Flow diagram of patient enrollment and analysis. ITT, intention-to-treat; PP, per-protocol.

proportions, and inter-group differences were assessed for significance using the chi-squared test. Continuous outcomes were reported as the median and interquartile range, and differences were assessed using the Mann-Whitney U test. Medication adherence, knowledge about cancer pain and pain medications, pain score, breakthrough pain, and QoL were compared between the two groups at baseline and week 4 on the intention-to-treat (ITT) population. Adverse events were analyzed in terms of frequency distributions on the PP population. If the proportion of missing data was greater than 40%, the data would not be included in the analysis, otherwise data were imputed using multiple imputation. Statistical calculations were performed using SPSS 23 (IBM, Chicago, IL, USA). A two-sided P value <0.05 was considered statistically significant.

## Results

From August 2018 to September 2019, we screened 402 outpatients with cancer pain for inclusion in this study, of which 118 were randomized into the intervention (n=60) or control (n=58) groups (*Figure 2*). One patient in the control group declined to participate in the baseline evaluation, so 117 patients were included in the ITT population. Finally, 102 patients (51 in each group) completed the 30-day follow-up and were therefore included in the PP population.

Baseline demographic, clinical, and pain-related characteristics were generally balanced between the intervention and control groups in the ITT population (*Table 1*). Most patients in the control (80.7%) and intervention (70.0%) groups were prescribed sustained-release oxycodone. The remaining patients were prescribed transdermal fentanyl and sustained-release morphine.

During the individualized care, pharmacists provided various interventions aimed at remedying the lack of knowledge among patients about pain treatment and medications, lack of awareness about the treatment adverse reactions, inadequate medication adherence, and inappropriate analgesic regimens (*Figure 3*). During the 4 weeks of interventions, only seven patients received all five interventions, while 10 patients received four interventions. The three most frequent interventions were educating

 

**Table 1** Baseline clinicodemographic characteristics of the included opioid-tolerant cancer outpatients

| Characteristics | Control group (n=57) | Intervention group (n=60) |
|---|---|---|
| Age (years) | 62.0 (55.5–68.0) | 61.5 (54.0–68.0) |
| Male | 37 (64.9) | 39 (65.0) |
| Primary diagnosis | | |
| Lung cancer | 23 (40.4) | 20 (33.3) |
| Colorectal cancer | 9 (15.8) | 8 (13.3) |
| Breast cancer | 1 (1.8) | 6 (10.0) |
| Esophageal cancer | 5 (8.8) | 2 (3.3) |
| Liver cancer | 4 (7.0) | 2 (3.3) |
| Gastric cancer | 2 (3.5) | 3 (5.0) |
| Other | 13 (22.8) | 19 (31.7) |
| Disease stage | | |
| II | 2 (3.5) | 4 (6.7) |
| III | 0 (0.0) | 1 (1.7) |
| IV | 55 (96.5) | 55 (91.7) |
| Karnofsky performance status score | | |
| 60 | 5 (8.8) | 10 (16.7) |
| 70 | 15 (26.3) | 15 (25.0) |
| 80 | 22 (38.6) | 26 (43.3) |
| 90 | 15 (26.3) | 9 (15.0) |
| Bone metastases | 28 (49.1) | 29 (48.3) |
| Pain type | | |
| Somatic | 16 (28.1) | 15 (25.0) |
| Visceral | 3 (5.3) | 9 (15.0) |
| Neuropathic | 1 (1.8) | 6 (10.0) |
| Mixed | 37 (64.9) | 30 (50.0) |
| Medications | | |
| Sustained-release oxycodone | 46 (80.7) | 42 (70.0) |
| Sustained-release morphine | 3 (5.3) | 6 (10.0) |
| Fentanyl patch | 8 (14.0) | 12 (20.0) |

Values are presented as n (%) or median (interquartile range).

the patients about pain treatment (n=58), education about pain medications (n=51), and resolving adverse drug reactions (n=33). Among all of the problems related to pain management that were explored in this study, the proportions of problems from baseline to week 4 were more prevalent in the individualized intervention group than in the control group (Table S3).

Between baseline and week 4, both groups showed a significant improvement in pain score, breakthrough pain frequency, and knowledge about pain treatment (*Table 2*). The proportion of patients adequately adhering to opioid medication increased from 68.6% to 84.3% in the intervention group and from 60.8% to 72.5% in the control group, and the rate of high adherence at 4 weeks was similar between the groups (P=0.149). The proportion of participants who experienced breakthrough pain declined markedly from baseline to week 4 in the intervention group (P=0.029), but not in the control group (P=0.322).

At week 4, knowledge about pain and medications was significantly greater in the intervention group than in the control group (P<0.001), and the intervention group showed a substantially lower pain score (P=0.015). The two groups did not differ notably in terms of the self-reported QoL (P=0.322) or the rates of adverse events (*Table 3*).

The oral morphine equivalent daily dose (OMEDD) was increased in both the control (median 120 *vs.* 120 mg, mean 153.5 *vs.* 168.8 mg) and intervention (median 90 *vs.* 120 mg, mean 120.0 *vs.* 145.1 mg) groups. However, there was no significant difference in OMEDD between the two groups at baseline (P=0.143) and at week 4 (P=0.283). And the increment of dose between two groups was also similar. (P=0.712).

## Discussion

In this study, we provided evidence that individualized pharmaceutical interventions, based on each patient's knowledge of pain and pain medications, can substantially improve pain control. Our study adds to a growing body of literature indicating that pharmacist-delivered interventions in patients with cancer pain can reduce the pain intensity and increase the level of knowledge related to pain management (19,20,27,28). Our findings validate the recommendations from the Chinese National Health Commission (42) and the US NCI (43,44) to include clinical pharmacists in cancer pain management.

A limited number of studies have investigated the role of pharmacists in the management of outpatients with cancer pain. Gagnon *et al.* (45) demonstrated that the participation of clinical pharmacists in palliative radiotherapy clinics plays a key role in holistic pain assessment and optimization

 

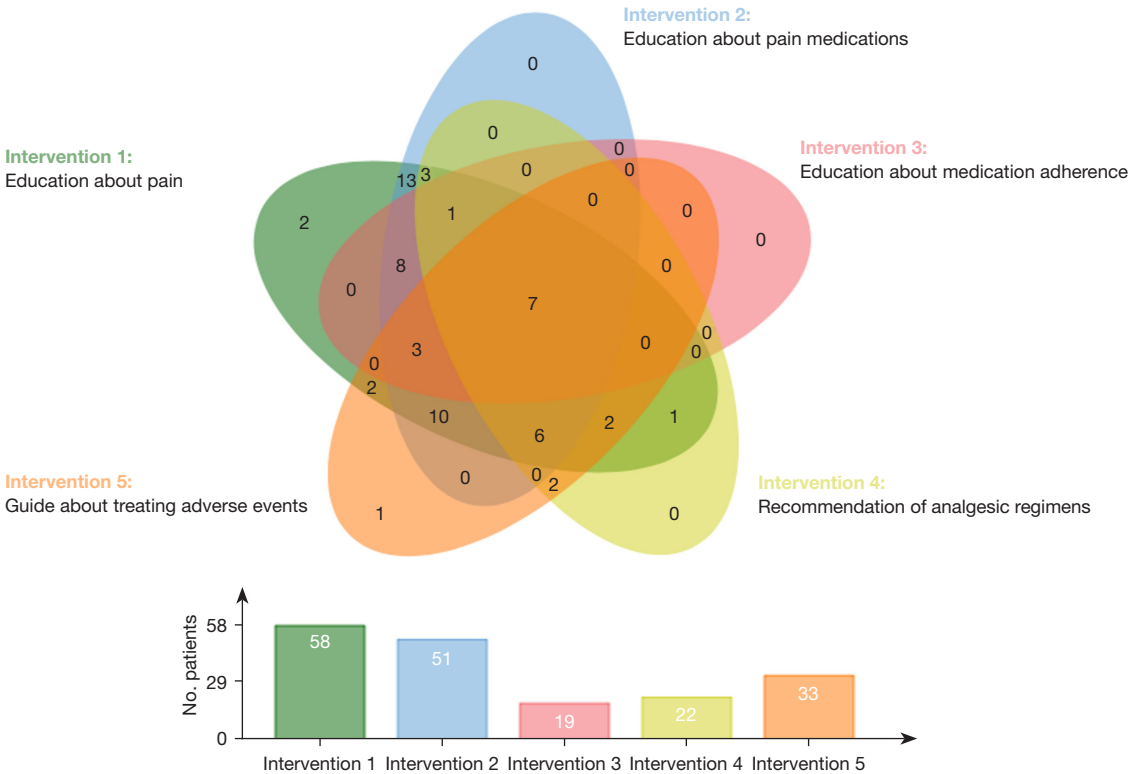


**Figure 3** The diverse interventions provided by pharmacists to the intervention group, and the numbers of patients receiving each intervention.

**Table 2** Intragroup and intergroup comparisons of the cancer pain-related outcomes in the control and intervention groups

| Outcome | Control group (n=51) | | | Intervention group (n=51) | | | P for comparison between the two groups at baseline | P for comparison between the two groups at week 4 |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Week 4 | P* | Baseline | Week 4 | P* | | |
| Patients reporting high adherence | 31 (60.8) | 37 (72.5) | 0.208 | 35 (68.6) | 43 (84.3) | 0.062 | 0.407 | 0.149 |
| Pain score | 3.0 (3.0–5.0) | 3.0 (3.0–3.0) | 0.001 | 3.0 (3.0–4.0) | 3.0 (2.0–3.0) | 0.000 | 0.817 | 0.015 |
| Patients with numerical rating scale score ≤3 | 28 (54.9) | 42 (82.4) | 0.003 | 27 (52.9) | 48 (94.1) | 0.000 | 0.843 | 0.065 |
| Frequency of breakthrough pain per week | 1.0 (0.0–10.0) | 0.0 (0.0–5.0) | 0.000 | 3.0 (0–10.0) | 0.0 (0.0–5.0) | 0.002 | 0.502 | 0.825 |
| Patients experiencing no breakthrough pain during 1 week | 22 (43.1) | 27 (52.9) | 0.322 | 19 (37.3) | 30 (58.8) | 0.029 | 0.545 | 0.550 |
| Level of knowledge about pain and pain medications | 7.0 (6.0–8.3) | 8.1 (6.3–9.4) | 0.000 | 6.4 (5.0–8.4) | 11.9 (9.9–12.6) | 0.000 | 0.402 | 0.000 |
| QoL | 0.769 (0.35–1.00) | 0.782 (0.11–1.00) | 0.390 | 0.775 (0.45–1.00) | 0.782 (0.11–1.00) | 0.162 | 0.732 | 0.871 |

Values are reported as n (%) or median (interquartile range), unless otherwise noted. *, comparison between baseline and week 4. QoL, quality of life.

**Table 3** Comparison of the medication-related adverse events between the control and intervention groups

| Adverse event | Control group (n=57) | Intervention group (n=60) | P |
|---|---|---|---|
| Constipation | 24 (42.1) | 24 (40.0) | 0.817 |
| Vomiting | 6 (10.5) | 5 (8.3) | 0.685 |
| Nausea | 6 (10.5) | 5 (8.3) | 0.685 |
| Somnolence | 2 (3.5) | 5 (8.3) | 0.271 |
| Urinary retention | 5 (8.8) | 2 (3.3) | 0.215 |
| Insomnia | 0 (0.0) | 1 (1.7) | 0.328 |
| Pruritus | 1 (1.8) | 0 (0.0) | 0.303 |
| Hoarseness | 1 (1.8) | 0 (0.0) | 0.303 |
| Sweating | 1 (1.8) | 0 (0.0) | 0.303 |
| Elevated liver function | 2 (3.5) | 0 (0.0) | 0.143 |
| Sychnosphygmia | 1 (1.8) | 0 (0.0) | 0.303 |
| Indigestion | 1 (1.8) | 0 (0.0) | 0.303 |
| Stomachache | 1 (1.8) | 0 (0.0) | 0.303 |
| Fatigue | 1 (1.8) | 0 (0.0) | 0.303 |
| Delirium | 1 (1.8) | 0 (0.0) | 0.303 |
| Dry mouth | 1 (1.8) | 0 (0.0) | 0.303 |
| Dizzy | 1 (1.8) | 0 (0.0) | 0.303 |
| Total | 32 (56.1) | 27 (45.0) | 0.228 |

Values are presented as n (%), unless otherwise noted.

of treatment options, contributing to improved symptom control of patients receiving palliative radiotherapy. Yamada *et al.* (30) evaluated the impact of continuous pharmaceutical interventions on pain management and opioid-induced adverse effects in outpatients with cancer. Their results indicated that pain intensities significantly decreased following continuous pharmacist intervention. However, these two studies did not confirm whether pharmacist interventions contribute to pain remission without a control group. We designed this prospective, multicenter, randomized controlled study and evaluated the effect of individualized pharmaceutical care in outpatients with cancer pain in terms of their knowledge about pain treatment, medication adherence, frequency of breakthrough cancer pain, and QoL as well as the pain score and adverse events.

Medication problems and patient outcomes may be improved more efficiently if the interventions are tailored to the patients' individual barriers (46). The individualized nature of the interventions in the present study meant that the patients received education and monitoring most closely suited to their specific pain management challenges. Thus, only seven patients received all five interventions that were planned in this study. The most frequent intervention in our study was education about pain and pain medications. The fact that many patients in our cohort did not require several of the other interventions may reflect that they had already received relevant education or pharmaceutical care.

Our results suggest that individualized pharmaceutical care can markedly reduce patient-related problems and significantly improve pain control for opioid-tolerant outpatients. At the same time, such care did not notably improve the adherence to opioid medication in our cohort. This apparently counterintuitive result may reflect the already high proportion of patients in our relatively small cohort who already had adequate adherence at baseline. It may also reflect the "Hawthorne effect", in which the baseline assessments of knowledge and medication adherence may have influenced the behavior of both the intervention and control groups (47). The Hawthorne effect may also help to explain why the control group showed improvement in medication adherence during the 4-week follow-up. Another possible explanation is that the OMEDD increased more in the intervention group than in the control group during the follow-up period. A fourth explanation is that the personalized follow-up by pharmacists fulfilled certain psychological and emotional needs in patients, which alleviated their perceived pain (48).

Our study has several limitations that should be noted. Firstly, we assessed the patients' knowledge about cancer pain and medications as well as the appropriateness of analgesic regimens using custom-designed questionnaires rather than standardized, validated instruments (Figure S1, Table S2). This may reduce the generalizability of our findings to other patient populations and healthcare contexts. Nevertheless, the questionnaires were developed by a multidisciplinary team of pain specialists and aligned with relevant national and international guidelines (49,50). Secondly, different pharmacists delivered interventions at the different study sites, although they followed the same overall intervention protocol. While variations in pharmacist attitudes and behaviors may have confounded our analysis, this situation reflects how interventions are deployed in the clinic, so our results are likely to have real-world relevance. Moreover, we did not perform corrections

 

for multiple comparisons.

## Conclusions

Our results suggest that individualized pharmaceutical care can markedly reduce patient-related problems and significantly improve pain control for opioid-tolerant outpatients. These findings validate the recommendations to include clinical pharmacists in the management of cancer pain.

## Acknowledgments

The authors would like to thank Tong YH for generating the random allocation sequence. We thank the participants of this study. The authors are grateful for support from the Eastern China Cooperative Oncology Pharmacy Group (ECCOPG).
*Funding:* This work was supported by Mundipharma (China) Pharmaceutical.

## Footnote

*Reporting Checklist:* The authors have completed the CONSORT reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4091/rc

*Trial Protocol:* Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4091/tp

*Data Sharing Statement:* Available at https://atm.amegroups.com/article/view/10.21037/atm-22-4091/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-4091/coif). All authors report that this study was sponsored by Mundipharma (China) Pharmaceutical. However, the sponsor did not participate in the conduct of the study and analysis of the data. The authors have no other 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. This study was performed in accordance with the Declaration of Helsinki (as revised in 2013), and all of the included research centers provided ethical approval. Also, all participants provided written informed consent.

*Permission:* We have received license for the use of the medication adherence scale (Morisky, Green, Levine Scale) from the copyright holder.



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(English Language Editor: A. Kassem)

**Cite this article as:** Ding H, Song Y, Wu N, Zheng X, Wei Q, Sun Y, Xie R, Zhai Q, Xu S, Qi Y, Wang Y, Li H, Yang L, Fan Q, Zhao Q, Chen J, Shi J, Duan C, Du Q, Zhang Y, Song Z, Fu S, Cai Y, Huang X, Fang L, Liu Y, Huang P. Impact of individualized pharmaceutical care on efficacy and safety of opioid-tolerant outpatients with cancer pain: a multicenter randomized controlled trial. Ann Transl Med 2022;10(18):989. doi: 10.21037/atm-22-4091

 