ANNALS OF PALLIATIVE MEDICINE

Peer Review File

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Detailed Responses to Review Comments A

General Comments:

Clinical pharmacy services based on the management of pharmacotherapy plays an essential role in cancer pain patients. This manuscript showed the benefit of CP in China patients. However, there are some points should be addressed before published.

Reply:

We thank the Reviewer for the positive comments on our study. We have followed your suggestions and made every possible effort to address the concerns. Detailed responses are below.

Major Comments:

Comment 1:

As this study has no control group, the "results part" of abstract should be better compared with normal value to see the improvement.

Reply 1:

As the Reviewer mentioned, the present study is a single-arm and pre-post study. The results revealed that clinical pharmacist' comprehensive interventions were efficacious in improving their medication adherence and pain relief, as well as reducing incidence of AEs for cancer pain patients. Future studies included control group will be conducted to verify these findings. This limitation has been added in the

limitation part as follows **(kindly see page 14, line 306)**: "Several limitations need to be considered. Firstly, no control group was involved. Thus, we compared our outcomes with those in similar programs in China and other countries. Further studies included control groups are necessary to be conducted."

Comment 2:

Line 136: How to calculate the score of 7 items (general activity, mood, walking ability, normal work, sleep, relations with other people and enjoyment of life)? Please add the reference.

Reply 2:

We appreciate the Reviewer for pointing out this issue. It is according to the National Comprehensive Cancer Network Adult Cancer Pain Guidelines (version 1.2018). As suggested, we have added the guideline as a reference **(kindly see page 8, line 170)**: "Pain-related interference of daily life (daily interference) was assessed through 7 items (general activity, mood, walking ability, normal work, sleep, relations with other people and enjoyment of life)."

Comment 3:

Some Tables should be considered as supplemental materials. Please rearrange it.

Reply 3:

We thank the Reviewer for the suggestive comments about our study. We have rearranged and shorten some tables.

Table 1 Baseline socio-demographics and clinical characteristics

Parameters	**Patients number (n=42)**

Age, mean years (SD)	59 (10)
Male gender (%)	28 (66.7%)
Education completed	
Primary/elementary school	9 (21.4%)
High school	31 (73.8%)
bachelor's degree or above	2 (4.8%)
ECOG PS	
0	1 (2.4%)
1	20 (47.6%)
2	10 (23.8%)
3	11 (26.2%)
Tumor types	
Esophageal carcinoma	9 (21.4%)
Lung cancer	8 (19.0%)
Cervical cancer	8 (19.0%)
pancreatic cancer	6 (14.3%)
Others	11 (26.2%)
Tumor stage	
Locally advanced cancer	4 (9.5%)
Metastatic cancer	38 (90.5%)

ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 2 Baseline pain-related characteristics

Parameters	**Patients number (n=42)**
Number of pain locations	
1	41(97.6%)

2	1(2.4%)
Pain sites	
Bone pain	14(33.3%)
Somatic pain	13(31.0%)
Visceral pain	12(28.6%)
Neuropathic pain	4(9.5%)
Initial analgesics	
Oxycodone sustained-release tablets	21(50%)
Morphine sustained-release tablets	12(28.6%)
Tramadol sustained-release tablets	5(11.9%)
Fentanyl transdermal patches	1(2.4%)
Oxycodone and Acetaminophen tablets	1(2.4%)
Morphine tablets	1(2.4%)
Ibuprofen capsules	1(2.4%)

Table 3 DRPs and Interventions from CP

Parameters	**Patients number**
DRPs (n=57)	
inadequate pain control	36(63.2%)
no attention paid to AE	9 (15.8%)
no opioids dosage reduction in time or opioids overdose	8 (14.0%)
inappropriate drugs	3(5.3%)
AE persist	1(1.8%)
Interventions from pharmacists (n=63)	

short-acting opioids administration	16(25.4%)
increasing the dose or frequency of long-acting opioids	13(20.6%)
combined with adjuvant analgesics	8 (12.7%)
initiating opioids	4(6.3%)
combined with medicines to relieve AE	9 (14.3%)
decreasing the dose or withdrawal opioids	8 (12.7%)
Switch to other medications	3(4.8%)
opioids rotation	1(1.8%)

DRPs: Drug Related Problems, AE: adverse events

Table 4 Pain intensity and Daily interference change

Items	**Baseline**	**Day3**	**Day7**	**Day14**	**Day28**
Pain intensity (mean ± SD)					
worst PI in last 24h	6.12±2.33	3.05±1.71	3.05±2.27*	2.27±1.73	2.22±1.69*
least PI in last 24h	1.69±1.73	0.43±0.94*	0.33±0.57*	0.20±0.51*	0.16±0.44
average PI in last 24h	3.96±1.77	1.85±1.29*	1.70±1.36*	1.26±0.99	1.14±0.95*
PI Right now	2.36±1.85	0.88±1.42*	0.62±0.70*	0.41±0.71*	0.38±0.72*
Daily interference (mean ± SD)					
General Activity	5.40±2.98	3.31±2.44*	3.10±2.55*	2.32±2.12*	2.22±2.12*
Mood	5.10±3.05	2.21±2.24*	1.86±2.27*	1.46±1.91	1.32±1.84*
Walking Ability	5.05±3.38	2.76±2.83*	2.43±2.70*	1.78±2.30*	1.68±2.29*
Normal Work	5.52±3.34	3.36±3.13*	3.02±3.08	2.41±2.73*	2.38±2.69*
Relations with other people	4.40±2.91	1.69±1.91*	1.43±1.81*	1.07±1.60*	0.92±1.44*
Sleep	5.19±2.93	2.33±2.18	1.98±2.39	1.24±1.64	1.05±1.56

Enjoyment of life	4.83±3.48	2.69±3.02*	2.26±3.03*	1.56±2.25*	1.65±2.29*

PI: Pain intensity, * p<0.01 compared with baseline.

Comment 4:

The authors must consider having a native English speaker, or English Language Editing Service – preferably with background in biology – to revise this work.

Reply 4:

We thank the Reviewer for pointing out language issue about our study. As suggested, we have invited a native speaker to make an improvement for our language and hope that the current version can meet the requirement for publication in ATM. The revised sentences are presented with red marks.

Detailed Responses to Review Comments B

Major Comments:

Comment 1:

The title seems grammatically incorrect, "management of pharmacotherapy" doesn't make sense; revising it to ".... role of clinical pharmacist in cancer pain pharmacotherapy".

Reply 1:

We thank the Reviewer for the suggestive comments about article title. As suggested, we have improved the title as follows: "Preliminary exploration on the role of clinical pharmacists in cancer pain pharmacotherapy"

Comment 2:

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I think the objective of the study was not well described in both abstract and the main text. This is a pre-post study, so the aim should not be to describe or explore a model of….

Reply 2:

We fully agree that the statement of aim was inappropriate and accordingly have revised as follows **(kindly see page 3, line 47)**: "In this article, we assessed medication adherence, pain relief, drug related problems (DRPs) and analgesics adverse events (AEs) in cancer pain patients based on a model of clinical pharmacy services." **(kindly see page 6, line 116)**: "Thus, this study aims to assess medication adherence, pain relief, DRPs and analgesics adverse events (AEs) in cancer pain patients based on a model of clinical pharmacy services. We present the following article in accordance with the STROBE reporting checklist."

Comment 3:

The scientific background and rationale for the study are not strong enough, such as more information is needed regarding the role of CPs in cancer care and treatment, what they mainly do, the impacts of their work on cancer pain management, synthesizing from international literature.

Reply 3:

As suggested, we have added more information regarding the role of CPs in cancer care and treatment from international literature **(kindly see page 6, line 110)**: "According to a Chinese study, participation by the pharmacist in the cancer pain multidisciplinary management team led to a marked reduction in most of the drug-related problems (DRPs) and a statistically significant change in pain score."

Comment 4:

Please explicate when the study was conducted in the design section.

Reply 4:

We accordingly have added the statements as follows **(kindly see page 6, line 123)**: "This study is a prospective, single-arm intervention trial done in a teaching hospital (Renji Hospital, School of Medicine, Shanghai Jiao tong University) between November, 2018 and November, 2019."

Comment 5:

In the procedure and intervention section, pain assessment was well described, however, interventions after assessment were just mentioned as "the CP provided personalized medication education……", which is unclear in terms of what exactly the CPs have done. As the service model, which is the intervention, is the core part of this project, so a clear description is needed, including how it was development, the content of the intervention, how to implement it, and how to evaluate its effects.

Reply 5:

We fully agree that the interventions need a clear description. As suggested, we have improved the statements as follows **(kindly see page 7, line 145)**: "For patients with good medication adherence (score≥6), we gave them a 10-minutes face-to-face medication education as well as an "education manual for pain patients" for reading by themselves. For those with weak medication adherence (score<6), we spent about 20 minutes for medication education, including detailed explaining the "education manual for pain patients". After initial medication education, reassessment of medication adherence, pain intensity (PI) and daily interference were done based on the project (medication adherence: at day 14 and 28; PI and daily interference: at day 3, 7, 14 and 28). During 28-day follow-up, patients were monitored for analgesic efficacy and safety every day during hospitalization, and were scheduled for receiving

medication education and reassessment of cancer pain via telephone weekly after discharge. In addition, possible DRPs were identified by the CP based on her daily ward rounds with physicians, examination of prescriptions, and patient-pharmacist interview. Accordingly, advices to optimize analgesic therapy were offered for physicians. All the DRPs and recommendations were documented, whether or not the physician chose to accept them."

Comment 6:

In lines 116 - 118, "during 28-day follow-up, patients were monitored for medical efficacy and safety…, and were scheduled for interview via telephone weekly after discharge", why patients were monitored for medical efficacy and safety? Is this a part of the intervention? In addition, what's the content and purpose of the interview?

Reply 6:

Actually, CP offered medication education to patients and monitored for analgesic efficacy and safety through face-to-face interview during their hospitalization, as well as via telephone after discharge. In this process, CP identified DRPs and provided advances for physicians concurrently. Accordingly, we have revised as follows **(kindly see page 7, line 152)**: "During 28-day follow-up, patients were monitored for analgesic efficacy and safety every day during hospitalization, and were scheduled for receiving medication education and reassessment of cancer pain via telephone weekly after discharge. In addition, possible DRPs were identified by the CP based on her daily ward rounds with physicians, examination of prescriptions, and patient-pharmacist interview. Accordingly, advices to optimize analgesic therapy were offered for physicians."

Comment 7:

The recruitment procedure of study participants was missing, such as the methods of selection of participants and methods of follow-up, and so on.

Reply7:

We accordingly have improved recruitment procedure of study participants as follows **(kindly see page 6, line 125)**: "The CP participated in daily ward rounds with physicians in department of radiation oncology, and new admitted patients were eligible for inclusion if they met the following criteria: 1) aged 18 years or older; 2) confirmed diagnosis of cancer; 3) diagnosis of nociceptive pain related to cancer or cancer therapy by the treating physician; 4) life expectancy of at least 3 months; 5) able to comprehend, speak, and read Chinese. Patients were excluded in case of invasive pain treatment (e.g., nerve block or patient-controlled analgesia). All patients have provided written informed consent."

Comment 8:

Please check and revise the format of statistical tables.

Reply 8:

Thanks for the suggestive comments, we have revised the format of all tables.

Comment 9:

It would be great if more information regarding the implication of this study could be provided.

Reply 9:

We thank the Reviewer for the suggestive comments about our study, and have added the statements as follows **(kindly see page 14, line 295)**: "Strengths of this study mainly include the clinical pharmacist's active role in cancer pain treatment. Ten-year work in department of radiation oncology enabled her abundant experience on dealing

with multiple links of cancer pain treatment. Her professional and meticulous pharmaceutical care has bridged the gap in doctors' treatment of cancer pain. The present study has preliminarily explored a model of comprehensive pharmaceutical service in cancer pain patients and proved its positive effect in clinical practice, which can be extrapolated to other centers. Furthermore, due to the combination of multiple drugs, patients with cancer pain are at a significant risk of DRPs, which cause or contribute to inadequate pain control or possible adverse events, making it urgent to resolve. As we reported, DRPs occurred in the course of cancer pain treatment but could have been ameliorated with CP's interventions."

Comment 10:

Generalizability of study results is another limitation.

Reply10:

We appreciate the Reviewer for pointing out this issue. Indeed, the present study is a single-arm, pre-post and preliminary study that assess the effect of clinical pharmacist' comprehensive interventions for cancer pain patients by improving their medication adherence and pain relief, as well as reducing incidence of AEs. Further randomized controlled trials will be conducted to facilitate validation of the conclusion and reassure that findings can be extrapolated to other centers.