Current Problems in Cancer 43 (2019) 77–85

Contents lists available at ScienceDirect

Current Problems in Cancer

journal homepage: www.elsevier.com/locate/cpcancer

Factors associated with optimal pain management in advanced cancer patients

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ARTICLE INFO

Keywords:
Advanced cancer
Analgesic effect
Chronic pain
Factors

ABSTRACT

Purpose: To analyze clinical factors that were associated with inadequate pain control in cancer patients with metastatic malignancy and moderate to severe baseline pain.
Patients: We retrospectively analyzed data from 260 advanced cancer patients who admitted to the First Hospital of Jilin University (Jilin, China) from January 2012-May 2013.
Measurements: Statistical analysis was performed to assess the correlation between pain control and baseline characteristics including, gender, patient age, type of malignancy, presence of bone metastases, pain intensity, pain location, etiology of pain, type of pain, and presence of breakthrough pain.
Main Results: A total of 75.4% of patients obtained satisfactory pain control (numerical rating scale ≤ 3) in 3 days. Baseline characteristics including gastrointestinal tumors ($P = 0.032$), severe pain ($P < 0.001$), and frequent breakthrough pain ($P < 0.001$) were independent risk factors of poor pain control in the 3-day treatment. These factors were also significantly associated with longer time needed to achieve stable pain control. Of the 185 patients treated with opioids, higher doses of analgesics were used in younger

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

☆☆ Conflicts of interest: The Authors declare that there is no conflict of interest.

☆☆☆ Ethics approval: Ethical approval was given by the Ethics Committee of the First Hospital of Jilin University, Changchun, China.

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https://doi.org/10.1016/j.currproblcancer.2018.05.002

patients (<60 years old; $P = 0.018$), and in patients with severe pain ($P < 0.001$), neuropathic pain ($P = 0.002$), and frequent breakthrough pain ($P = 0.015$).

Conclusions: Factors associated with more difficult pain control include gastrointestinal tumor, severe baseline pain, presence of breakthrough pain, and neuropathic etiology of pain.

Introduction

Cancer pain is extremely prevalent and can have profound psychological and physical impact on the patient. Approximately 70% of patients with advanced cancer experienced chronic pain[1] and the prevalence increases to 80%-90% in terminal, end-stage disease.[2] Although cancer pain guidelines are available, adequate pain control in this population often remains clinically challenging.[2] Cancer pain is a complex, heterogeneous entity that can be produced by multiple etiologies and mechanisms.[3-6] Cancer pain can be classified according to its location, involved organ and/or tissue system, temporal pattern, severity, and mechanism. Cancer pain can be nociceptive arising from somatic or visceral structures, neuropathic or mixed type etiology. It is paramount to perform a comprehensive clinical evaluation of pain in cancer patients, which may provide invaluable information about disease progression. Moreover, an understanding of the pathophysiological characteristic of cancer pain may influence analgesic treatment selection as different types of pain have different sensitivities to distinct classes of analgesics. The Edmonton Classification System for Cancer Pain is a standardized assessment aid to categorize cancer pain and guide clinical management.[7-10] Previous studies have found associations between uncontrolled pain and young patient age, neuropathic pain, high baseline pain intensity, and presence of incidental pain.[7-9,11,12] Our understanding of the pathogenesis of poorly controlled cancer pain has expanded greatly over the past couple decades. However, there is a paucity of data specifically studying cancer populations in the Asian-Pacific region.[13] Our study provides additional insight into the risk factors of inadequately controlled cancer pain in an inpatient Chinese hospital setting.

Methods

Patients

We retrospectively review the records of patients who were diagnosed with advanced cancer at the First Hospital of Jilin University (Jilin, China) from January 2012-May 2013. Of these patients, 105 are male and 91 are female, with median age of 57 years old. A total of 106 patients were ≥60 years old and 154 patients were <60 years old. These patients were selected for this study based on the main inclusion criteria, including (1) pathologic or cytologic diagnosis of solid malignancies; (2) tumor, node, and metastasis stage IV cancer; (3) accompanied with chronic moderate pain; (4) patients were conscious; (5) no opioid drug abuse; (6) no history of mental and neurologic disorders. The main exclusion criteria include (1) clinically significant diseases such as cardiovascular, hepatic, or renal disorder; (2) history of clinically significant psychiatric disease; (3) conditions which may interfere with the patient's ability to comply with the protocol requirements; (4) concurrent oncological treatments (eg, radiation therapy and chemotherapy) aiming to control acute pain. A total of 262 patients were admitted for inpatient care, but two of them died in a week after admission; their data were excluded from the analyses. The following demographic and clinical characteristics of the 260 patients were collected:

sex, age, cancer type, bone metastases status, characteristics of pain (ie, pain intensity, locations of pain, cause of pain, frequency of pain, mechanism of pain, and presence and/or absence of breakthrough pain), total morphine equivalent daily dose (MEDD) of opioid, and outcome of pain control after 3- and 7-day treatment.

The presence of tumor invasion was determined by magnetic resonance imaging or computed tomography. The neuropathic pain was screened using the screening questionnaire, ID pain,[14] and the diagnosis was based primarily on the criteria presented by the International Association of Pain Research in 2008: (1) the location of neuropathic pain is neuroanatomically logical; (2) the history suggested a relevant lesion or disease; (3) additional assessments confirming the pain located neuroanatomically; and (4) additional test confirming a lesion or disease explaining neuropathic pain. Patients fulfilled all the four criteria were diagnosed as definite neuropathic pain. Patients fulfilled the first 2 criteria in addition to criteria number 3 or 4; they were diagnosed as high chance of neuropathic pain. Patients who only fulfilled the first 2 criteria were diagnosed as possible neuropathic pain. We define all these patients had neuropathic pain in this study. The study was approved by the Ethics Committee of the First Hospital of Jilin University, and all patients had informed consent signed. The Strengthening the Reporting of Observational Studies in Epidemiology guideline for cohort study has been followed.

Measures

Patients provided daily pain intensity rating using numerical rating scale. Scores 1-3 are mild pain, scores 4-6 are moderate pain, and 7-10 are severe pain. Analgesic treatments were given in accordance with the Comprehensive Cancer Network Guidelines for Adult Cancer Pain.[15] Starting dose of morphine hydrochloride was 5-15 mg, administered orally in every 4 hour. The dose was then adjusted appropriately according to the response of the patients. For opioid tolerant patients, the starting dose was determined in reference to the patients' medication history. In an occurrence of breakthrough pain, rescue doses at 10%-20% of the total daily dose of hydromorphone were given. After dosage titration was accomplished, sustained release opioid was given. Concurrent nonsteroidal anti-inflammatory drugs were administered if there were no contraindications or intolerances. If medication could not be administered orally, other routes (eg, transdermal patches or intravenous) were used, and the dosage was converted to equivalent oral dosage for analysis. The conversion was performed according to the Comprehensive Cancer Network guideline. Outcome of pain control was defined as satisfactory if numerical rating scale declined to $\leq$3, breakthrough pain $\leq$3 times/day, and pain management $\leq$3 times/day. Otherwise, the outcome of pain control was defined as poor.

Statistical analysis

Univariate and multivariate logistic regressions were performed in analyzing the associations of clinical-pathologic factors and pain control after 3-day treatment. Univariate and multivariate Cox regression analysis was used to identify the associate variables and outcome of pain control. Rank sum test was used to compare if there were differences in dosage given between groups: Mann-Whitney test was used for comparison between 2 groups and Kruskal-Wallis was used for comparison with 3 or more groups. SPSS 17.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

Results

Baseline characteristics

The study consisted of 260 patients. Various types of malignancies were found in the patient cohort, including lung cancer (112/260, 43%), gastrointestinal cancer (81/260, 31%), and others

(including breast cancer, liver cancer, pancreatic cancer, and cervical cancer; 67/260, 26%). And about half of the patients (46.5%) had bone metastases. Most patients exhibited moderate pain (66.5%), while others reported to have severe pain (33.5%). The majority of the patients reported chest or back pain (75.4%), and others reported pain in other parts of the body (24.6%). The main cause of pain was tumor invasion (98.5%). Different types and characteristics of pain were reported, including neuropathic pain (46.2%) and frequent breakthrough (≥3 times per day; 33.1%).

Treatment information

The median onset of adequate analgesia was 2 days. The 3-day treatment provided satisfactory pain control in 75.4% of the patients, and the 7-day treatment provided satisfactory pain control in 81.9% of the patients. The majority of the patients (71.2%) were treated with opioid. Oral dosing (91.2%) is the main administration route, with others administered through intravenous (1.9%) or transdermal patches (6.9%). Combination therapy with nonsteroidal anti-inflammatory drugs was used in 19.2% of patients.

Outcome of 3-day pain control treatment

The associations between the outcome of pain control after 3-day treatment and various clinical factors were summarized in Table 1. Univariate logistic regression analysis showed that gastrointestinal cancer ($P = 0.015$), severe pain ($P = 0.000$), neuropathic pain ($P = 0.015$), and frequent breakthrough pain ($P = 0.000$) were risk factors of poor pain control. Multivariate logistic regression analysis showed that gastrointestinal cancer (odds ratio [OR] = 2.438, 95% confidence interval [CI]: 1.082 ~ 5.495, $P = 0.032$), severe pain (OR = 3.638, 95% CI: 1.865 ~ 7.095, $P < 0.001$), and frequent breakthrough pain (OR = 3.349, 95% CI: 1.727 ~6.495, $P < 0.001$) were independent risk factors associated with poor pain control. Sex, age, presence of bone metastases, locations of pain, and cause of pain were not significantly associated with pain control outcome in both types of analysis ($P > 0.05$).

Time needed to achieve pain control

Cox regression analysis showed that gastrointestinal cancer (hazard ratio [HR] = 0.680, 95% CI: 0.469 ~0.986, $P = 0.042$), severe pain (HR = 0.569, 95% CI: 0.398 ~0.815, $P = 0.002$), and frequent breakthrough pain (HR = 0.645, 95% CI: 0.457 ~0.911, $P = 0.013$) were independent risk factors for longer time of pain control treatment. Sex, age, presence of bone metastases, locations of pain, cause of pain, and presence of neuropathic pain were not associated with the time needed for pain treatment (Table 2).

Effects of opioid doses

The opioid doses were transformed into MEDD for analysis. Clinical factors including younger age (<60 years old; $P = 0.018$), severe pain ($P < 0.001$), neuropathic pain ($P = 0.002$), and frequent breakthrough pain ($P = 0.015$) were associated with higher doses of opioid. No significant differences in MEDD were found in patients with different sex, cancer type, cause of pain, locations of pain, and presence and/or absence of bone metastases ($P > 0.05$; Table 3).

Table 1
Associations of clinical characteristics and 3-day pain control evaluated with univariate and multivariate logistic regression analysis.

Characteristics	Rate of 3-day pain well controlled, *n* (%)	Univariate		Multivariate	
		OR (95% CI)	*P*	OR (95% CI)	p
Sex					
Male	105 (72.9)	1.000		1.000	
Female	91 (78.4)	0.740 (0.4161.315)	0.304	1.040 (0.5242.006)	0.910
Age (year)					
<60	112 (72.7)	1.000		1.000	
≥60	84 (79.2)	0.698 (0.388-1.258)	0.232	0.734 (0.370-1.458)	0.377
Cancertype					
Lung	93 (83.0)	1.000		1.000	
Gastrointestinal	55 (67.9)	2.314 (1.173-4.563)	0.015	2.438 (1.082-5.495)	0.032
Others	48 (71.6)	1.937 (0.938-4.001)	0.074	1.437 (0.625-3.302)	0.393
Bone metastases					
Absent	109 (78.4)	1.000		1.000	
Present	87 (71.9)	1.420 (0.806-2.501)	0.225	1.791 (0.871-3.685)	0.113
Pain intensity					
Moderate	149 (86.1)	1.000		1.000	
Severe	47 (54.0)	5.284 (2.891-9.656)	0.000	3.638 (1.865-7.095)	0.000
Location of pain					
Chest or back	153 (78.1)	1.000		1.000	
Limbs	43 (67.2)	1.738 (0.933-3.236)	0.082	1.390 (0.647-2.985)	0.398
Cause for the pain					
Not tumor invasion and metastasis	3 (75.0)	1.000		1.000	
Tumor invasion and metastasis	193 (75.4)	0.979 (0.100-9.583)	0.986	0.214 (0.019-2.385)	0.210
Neuropathic pain					
Absent	114 (81.4)	1.000		1.000	
Present	82 (68.3)	2.032 (1.145-3.607)	0.015	1.664 (0.836-3.313)	0.147
Frequent severe pain					
Absent	147 (84.5)	1.000		1.000	
Present	49 (57.0)	4.111 (2.274-7.432)	0.000	3.349 (1.727-6.495)	0.000

Discussion

Chronic cancer pain is one of the common symptoms in patients with malignant tumors, and unrelieved pain could substantially affect patients' quality of life. Although cancer can be a terminal disease, every effort should be made to prevent needless suffering. Pain relief has become a key task in palliative care. The 2011 European palliative treatment association suggested the use of pain intensity, pain mechanism, breakthrough pain, and anxiety as prognostic factors for outcome of pain control. In the Edmonton pain evaluation system, it is suggested that breakthrough pain, neuropathic pain, anxiety, addictive behavior and cognition function are prognostic factors of treatment outcome. The studies used to support these guidelines and systems were mostly conducted in European countries.[7-10] In the present study, we provided analyses of data from 260 Chinese patients and suggested clinical characteristics that were associated with the outcome of pain control.

The present study showed that clinical characteristics including severe pain, gastrointestinal cancer, and frequent breakthrough pain were independent risk factors for poor outcome of 3-day pain treatment. Pain intensity has been suggested as one of the important factors that should be considered when planning treatment strategy. In a multicenter study, Fainsinger et al showed that moderate to severe pain required longer time, more adjuvants, and higher final opioid doses than mild pain to achieve stable pain control.[9] In another study, Kaasa et al also suggested that severe pain was prognostic to the poor treatment outcome,[16] which is in accordance to our findings.

Table 2
Associations of clinical characteristics and time required for pain control evaluated with univariate and multivariate Cox regression analysis.

Characteristics	Median of analgesic effect time (days)	Univariate		Multivariate	
		HR (95% CI)	*P*	HR (95% CI)	*P*
Sex					
Male	3.0	1.000		1.000	
Female	2.0	1.175 (0.887-1.557)	0.262	1.042 (0.7741.404)	0.785
Age (year)					
<60	2.0	1.000		1.000	
≥60	2.0	1.116 (0.841-1.481)	0.447	1.075 (0.804-1.438)	0.625
Cancer type					
Lung	2.0	1.000		1.000	
Gastrointestinal	3.0	0.698 (0.499-0.975)	0.035	0.680 (0.469-0.986)	0.042
Others	2.0	0.813 (0.574-1.153)	0.245	0.891 (0.620-1.280)	0.533
Bone metastases					
Absent	2.0	1.000		1.000	
Present	2.0	0.869 (0.656-1.153)	0.331	0.749 (0.546-1.028)	0.073
Pain intensity					
Moderate	2.0	1.000		1.000	
Severe	4.0	0.478 (0.342-0.667)	0.000	0.569 (0.398-0.815)	0.002
Location of pain					
Body	2.0	1.000		1.000	
Limbs	2.0	0.857 (0.677-1.203)	0.373	0.972 (0.669-1.411)	0.880
Cause for the pain					
Not tumor invasion and metastasis	2.5	1.000		1.000	
Tumor invasion and metastasis	2.0	0.982 (0.314-3.017)	0.975	1.636 (0.509-5.259)	0.409
Neuropathic pain					
Absent	2.0	1.000		1.000	
Present	2.0	0.800 (0.602-1.062)	0.123	0.878 (0.644-1.197)	0.410
Frequent severe pain					
Absent	2.0	1.000		1.000	
Present	4.0	0.542 (0.391-0.751)	0.000	0.645 (0.457-0.911)	0.013

About one-third of the patients in the present study had gastrointestinal cancer; and it is a risk factor for poor outcome of pain control. The findings suggested that, in the absence of obstruction of the organ or lumen, the larger size of the visceral malignancy, the higher severity of the pain. Patients with gastrointestinal cancer usually have visceral pain, hypersensitive, and poor response to standard analgesics. Neuro block medication (such as abdominal cavity plexus block: celiac plexus block, hypogastric plexus block, and ganglion impar block) and other interventional therapy may be needed. Moreover, these patients often have poor gastrointestinal tolerability of opioid, which may lead to poor pain control. Knudsen et al suggested that pain in patients with lung cancer is more difficult to control, which is different from the finding in this study.[17] Further investigation will be needed to understand how the cancer types affect efficacy of pain control medication.

Breakthrough pain is a sudden increase of pain that may occur with different triggers, such as stress, illness, and certain activities. Most patients with cancer pain suffer from breakthrough pain, in which the pain intensity is usually severe. Fainsinger et al showed that median final opioid dose required to achieve stable pain control in patients with breakthrough pain was 60 mg, while it was 32 mg in patients without breakthrough pain.[9] In the study, breakthrough pain was also associated with longer time and more adjuvants to reach stable pain control. Recently, studies have shown that fentanyl pectin nasal spray and sublingual spray were well tolerated and provided faster onset of analgesia.[18,19] These medications may be considered during planning of treatment strategy.

Table 3
Comparison of final MEDD in patients administered with opioids.

Characteristics	Median of MEDD (25%-75%, mg)	*P*
Sex		0.051
Male	75.0 (40.0-120.0)	
Female	60.0 (40.0-80.0)	
Age (year)		0.018
<60	60.0 (40.0-100.0)	
≥60	60.0 (20.0-80.0)	
Cancertype		0.974
Lung	65.0 (40.0-80.0)	
Gastrointestinal	60.0 (40.0-100.0)	
Others	60.0 (40.0-105.0)	
Bone metastases		0.323
Absent	60.0 (40.0-80.0)	
Present	65.0 (40.0-80.0)	
Pain intensity		0.000
Moderate	40.0 (20.0-80.0)	
Severe	80.0 (60.0-160.0)	
Location of pain		0.509
Body	60.0 (40.0-80.0)	
Limbs	80.0 (40.0-80.0)	
Reasons for the pain		0.991
Not tumor invasion and metastasis	80.0 (30.0-80.0)	
Tumor invasion and metastasis	60.0 (40.0-80.0)	
Neuropathic pain		0.002
Absent	50.0 (20.0-80.0)	
Present	80.0 (40.0-95.0)	
Frequent severe pain		0.015
Absent	60.0 (40.0-80.0)	
Present	80.0 (37.5-142.5)	

Our study showed that younger patients (<60 years old), with severe pain, neuropathic pain, and frequent breakthrough pain required higher doses of analgesics. Patients at different age groups have different tolerability to pain and thus the different outcome of pain control. Green et al showed that middle-aged patients have higher occurrence of cancer pain than old-aged patients.[20] Gagliese et al also suggested that older patients accepted pain as an inevitable part of cancer and adapted better than younger patients despite comparable pain intensity and interference.[21] Therefore, elderly cancer patients may require a lower amount of analgesia than younger adults.[22] Neuropathic pain is caused by peripheral or central nervous system injury, leading to firing of abnormal nerve impulses. Previous studies have regarded neuropathic pain as a refractory pain index. Sometimes neuropathic pains show little response to nonopioid and opioid analgesics, but may be eased by tricyclic antidepressants and anticonvulsants. A systematic review has shown a favorable association in pain control with anticonvulsants or antidepressants when compared to control.[23] In the present study, clinical factors, younger age (<60 years old), and neuropathic pain were associated with the high MEDD. However, in multivariate regression analysis, such factors were not found to be associated with the outcome of 3-day treatment. Further studies will be needed to understand how these 2 factors are associated with doses of analgesics and pain control outcome.

Other clinical factors including, sex, presence of bone metastases, locations of pain, and cause of pain (ie, whether the pain was due to tumor invasion and metastasis) were not significantly associated with the outcome of pain control. Fainsinger et al and Knudsen et al also suggested that sex was not associated with the outcome of pain control. Pain control for patients with bone metastases was satisfactory, it is possible that analgesia combined with radiotherapy and bisphosphonate can effectively alleviate bone pain.[9,17]

The current study has its limitations, for example, the patient population has limited diversity (~75% of patients with lung or gastrointestinal cancer), and subgroup analysis was not performed to investigate the psychological factors that may influence the treatment response.[24] Although the eligibility criteria were in place to optimize the homogeneity of the patient population, viabilities in referral characteristics may still exist (eg, the use of nonstandardized previously). The treatment period is relatively short, from 3-7 days; further studies with a longer treatment time will help to evaluate if the results from current study is generalizable over longer durations of months to years. In conclusion, clinical characteristics including gastrointestinal tumor, severe pain, breakthrough pain, and neuropathic pain showed as main risk factors that affect outcome of pain control. These factors were associated with both poor pain control and prolonged time to achieve adequate control of pain. The prognostic factors may need to be taken into consideration when planning for pain management for advanced cancer patients.

Declaration

Ethics approval

Ethical approval was given by the Ethics Committee of the First Hospital of Jilin University, Changchun, China.

Consent for publication

All patients gave their written information consent.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JC contributed to the study design; NW, YD, LZ, HZ, and WL collected the data and performed the data analysis. All authors prepared the manuscript. NW, YD, and LZ revised the article critically.

Acknowledgment

This study is supported by the outstanding young teacher training program of Jilin University (419080500356).

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