RESEARCH ARTICLE

Determinants of Opioid Efficiency in Cancer Pain: a Comprehensive Multivariate Analysis from a Tertiary Cancer Centre

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Abstract

__Background__: Pain is one of the most terrifying symptoms for cancer patients. Although most patients with cancer pain need opioids, complete relief of pain is hard to achieve. This study investigated the factors influencing persistent pain-free survival (PPFS) and opioid efficiency. __Materials and Methods__: A prospective study was conducted on 100 patients with cancer pain, hospitalized at the medical oncology clinic of Akdeniz University. Patient records were collected including patient demographics, the disease, treatment characteristics, and details of opioid usage. Pain intensity was measured using a patient self-reported visual analogue scale (VAS). The area under the curve (AUC) reflecting the pain load was calculated from daily VAS tables. PPFS, the primary measure of opioid efficacy, was described as the duration for which a patient reported a greater than or equal to two-point decline in their VAS for pain. Predictors of opioid efficacy were analysed using a multivariate analysis. __Results__: In the multivariate analysis, PPFS was associated with the AUC for pain (Exp (B)=0.39 (0.23-0.67), *P*=0.001), the cumulative opioid dosage used during hospitalisation (Exp (B)=1.00(0.99-1.00), *P*=0.003) and changes in the opioid dosage (Exp (B)=1.01 (1.00-1.01), *P*=0.016). The change in VAS score over the standard dosage of opioids was strongly associated with current cancer treatment (chemotherapy *vs.* others) (ß=-0.31, T=-2.81, *P*=0.007) and the VAS for pain at the time of hospitalisation (ß=-0.34, T=-3.07, *P*= 0.003). __Conclusions__: The pain load, opioid dosage, concurrent usage of chemotherapy and initial pain intensity correlate with the benefit received from opioids in cancer patients.

Keywords: Cancer pain - chemotherapy - opioids - multivariate analysis

Introduction

Cancer-related pain is one of the most important symptoms that lowers the patients quality of life (Green et al., 2011). Approximately 50 % of patients with cancer experience pain (van den Beuken-van Everdingen et al., 2007; Aslan et al., 2011). The basis of analgesic therapy is the three-step analgesic ladder on the top of which are the drugs belonging to the group of strong opioids. Opioids are the basis of treatment of moderate to severe pain and nearly % 75 of patients require opioid therapy (Thapa et al., 2011). However complete pain relief is rarely achieved, and cancer-related pain remains undertreated throughout the world (Azevedo Sao Leao Ferreira et al., 2006; Brant 2010). The failure to manage pain properly is due to suboptimal usage of opioids because of several factors including limited resources, legal restrictions, failure to follow existing guidelines and patient related

factors (Davis and Walsh, 2004) as well as the lack of physician education (Budkaew and Chumworathayi, 2013) Beliefs about pain and opioids demonstreated a significant relationship with patients' opioid adherence (Liang et al., 2013; Colak et al., 2014).

In cancer patients with pain, identifying factors that predict the need for higher doses of opioids or characterize patients whose pain level will be stabilized by a given dosage of pain medications is an important step toward optimal pain control. The Edmonton classification system for cancer pain (ECS-CP) reflects that pain mechanism, incident pain, physiological distress, addictive behaviours and cognitive function are predictors of pain complexity (Fainsinger et al., 2005; Fainsinger et al., 2008). Although it is not taken into account in the ECS-CP system, pain intensity is also a negative predictor for pain control (Fainsinger et al., 2009). However, pain complexity and the heterogeneity of patient response to opioid analgesics

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are important barriers for optimal pain control in cancer patients. Therefore, the objective of this study is to identify additional factors that may influence pain-free survival as well as factors that are predictive of patient response to opioid analgesics.

Materials and Methods

Patients

The study population included 100 cancer patients who were hospitalised at the medical oncology clinic of Akdeniz University between August 2009 and January 2010. Patients were included in the study, whether they were hospitalized for pain palliation or another reason, if they reported cancer related pain regardless of pain medications they were using. Patient records were collected for information regarding patient age, gender, occupation, social support, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, nutritional status, cancer type, stage, details of previous therapies, reason for hospitalisation, pain localisation, pain treatment details and opioid dosage used.

Evaluation of pain and measurement of opioid efficacy

Patients asked to report their pain intensity every morning by the nursing staff during the hospitalisation period. The level of pain perception was measured by a patient self-reported visual analogue scale (VAS) for pain intensity on a scale from 0 to 10. Pain burden was defined as the area under the curve (AUC) calculated from VAS-time tables (Parruti et al., 2010). The total opioid dosage was calculated as the total amount of morphine used during hospitalisation including oral, transdermal and parenteral forms. A previously published conversion table was employed to express the opioid dosage in terms of parenteral morphine (Gammaitoni et al., 2003). The primary outcome of opioid efficacy was persistent pain-free survival (PPFS), which was defined as the time during which a patient reported greater than or equal to two-point decline in their VAS for pain. Changes in the VAS score while receiving the standard dosage of opioids was used as the secondary indicator of opioid efficacy. The change in VAS score with each 10-mg increase of parenteral morphine was calculated using the following equation for each patient:

$$\frac{\Delta \text{ VAS}}{\Delta \text{ morphine dosage* /10}}$$

* morphine dosage per day at the time of hospitalisation

Table 1. Persistent Pain-Free Survival after Hospitalisation in Cancer Patients with Pain

Factors	Univariate		Multivariate	
	Exp (B)	P	Exp (B) (95% CI)	P
Patient Factors				
Age	1.02	0.156		
Gender (male *vs*. female)	1.55	0.142		
Education**	1.09	0.652		
Social Support (from 1st degree relative *vs*. others)	1.62	0.31		
Occupational status				
private work *vs*. others	0.82	0.498		
governmental work *vs*. others	1.52	0.387		
lnBMI£	0.64	0.424		
ECOG**	1.27	0.111		
Nutrition Status (oral route *vs*. others)	1.31	0.329		
Disease and Treatment-Related Factors				
Diagnosis				
lung cancer *vs*. others	0.71	0.308		
GI cancer *vs*. others	1.04	0.907		
Stage (4 *vs*. others)	0.73	0.438		
Previous Radiotherapy (present *vs*. absent)	0.98	0.928		
Previous Chemotherapy (present *vs*. absent)	1.33	0.373		
Previous Surgery (present *vs*. absent)	1.63	0.082	1.24	0.488
Current Treatment (chemotherapy *vs*. others)	1.17	0.59		
Reason for Hospitalisation				
palliation for pain *vs*. others	1.63	0.165		
chemotherapy or radiotherapy *vs*. others	1.30	0.472		
Other Major Clinical Problems (present *vs*. absent)	1.30	0.479		
Pain-Related Factors				
Cause of Pain (bone metastasis *vs*. others)	0.89	0.678		
Pain localisation				
thorax *vs*. others	0.54	0.137		
abdomen *vs*. others	0.70	0.356		
Use of adjuvant analgesics				
(present *vs*. absent)	0.97	0.919		
VAS for pain at hospitalisation	0.88	0.054	0.87	0.1
Type of analgesics used prior to hospitalisation (opioids *vs*. others)	1.62	0.083	0.53	0.076
Opioid dose at hospitalisation	1.00	0.923		
VASmax for pain	0.82	0.011	1.19	0.177
lnAUCβ for pain	0.42	<0.001	0.39(0.23-0.67)	0.001
Cumulative opioid dose used during hospitalisation	1.00	0.001	1.00(0.99-1.00)	0.003
Change in opioid dose	1.00	0.055	1.01(1.00-1.01)	0.016

a*Survival after hospitalisation with 2 points or more decline in VAS for pain, **ordinal variable, £natural logarithmic transformation of body mass index, βnatural logarithmic transformation of area under curve of VAS for pain and time

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(mg) - morphine dosage per day at the time of discharge or death (mg).

Statistics

The statistical significance of the associations between the PPFS and the analysed factors was evaluated by univariate analysis. Factors with P-values less than 0.10 were then tested in a multivariate Cox-regression analysis using a forward stepwise procedure. BMI and AUC were logarithmically transformed prior to their inclusion in the analysis. Similarly, changes in the VAS while receiving the standard dosage of opioids and its relationship with the factors tested was first evaluated by univariate linear regression analysis, followed by multivariate linear regression analysis using a forward stepwise procedure for factors with P-values less than 0.10. Factors with P-values ≤0.05 in the multivariate analysis were considered statistically significant.

Results

General characteristics

Of the 100 patients included in the present study, 63 were male, 37 were female, and the median age of all patients was 56. The most common cancer diagnoses were lung (30%), gastrointestinal (28%), breast (9%) and

gynaecologic (9%) cancers, and 89% of patients were diagnosed with tumour metastasis. The most common reason for hospitalisation was pain palliation (28%). The most frequent aetiology of patient pain was visceral metastasis (62%). The mean VAS at hospitalisation and discharge were 4.05 and 1.94, respectively.

Adjuvant analgesics were included in the treatment regimen for 62% of patients, and the mean opioid dosage at the time of hospitalisation was 39.31±65.41 milligrams of morphine.

Predictors of opioid efficacy

The univariate analysis showed that the PPFS was significantly associated with the maximum VAS (Exp (B)=0.82, P=0.011), the AUC for pain (Exp (B)=0.42, P<0.01) and the cumulative opioid dosage used during hospitalisation (Exp (B)=1, P=0.001). The multivariate analysis revealed that AUC for pain (Exp (B)=0.39 (0.23-0.67), P=0.001), cumulative opioid dosage used during hospitalisation (Exp (B)=1.00 (0.99-1.00), P=0.003) and changes in the opioid dosage (Exp (B)=1.01 (1.00-1.01), P=0.016) were independent factors related to PPFS. Table 1 shows the PPFS after hospitalisation in cancer patients with pain.

The univariate analysis demonstrated that changes in VAS score while receiving the standard dose of

Table 2. Factors Associated with Change in Pain Score (VAS) while Receiving a Standard dose of Opioids

Factors	Univariate			Multivariate		
	Beta	t	P	Beta	t	P
Patient Factors						
Age	0.02	0.12	0.902			
Gender (male *vs.* female)	0.09	0.73	0.469			
Education**	0.04	0.34	0.735			
Social support (from 1st degree relative *vs.* others)	-0.03	-0.20	0.842			
Occupation status						
private work *vs.* others	-0.18	-1.36	0.180			
governmental work *vs.* others	-0.05	-0.38	0.707			
lnBMI£	-0.11	-0.83	0.410			
ECOG**	0.12	0.99	0.327			
Nutrition Status (oral route *vs.* others)	0.08	0.67	0.507			
Disease and Treatment-Related Factors						
Diagnosis						
lung cancer *vs.* others	-0.14	-1.02	0.313			
GI cancer *vs.* others	-0.29	-2.11	0.039	-0.18	-1.60	0.115
Stage (4 *vs.* others)	-0.24	-1.94	0.057	-0.18	-1.63	0.108
Previous Radiotherapy (present *vs.* absent)	0.16	1.30	0.200			
Previous Chemotherapy (present *vs.* absent)	0.06	0.49	0.626			
Previous Surgery (present *vs.* absent)	0.04	0.32	0.747			
Current Treatment (chemotherapy *vs.* others)	-0.34	-2.89	0.005	-0.31	-2.81	0.007
Reason for Hospitalisation						
palliation of pain *vs.* others	-0.02	-0.17	0.867			
chemotherapy or radiotherapy *vs.* others	-0.14	-1.07	0.290			
Other Major Clinical Problems (present *vs.* absent)	-0.07	-0.55	0.586			
Pain-Related Factors						
Cause of Pain (bone metastasis *vs.* others)	0.038	0.30	0.764			
Pain localisation						
thorax *vs.* others	-0.07	-0.39	0.697			
abdomen *vs.* others	-0.30	-1.56	0.115			
Use of adjuvant analgesics (present *vs.* absent)	0.09	0.75	0.458			
VAS for pain at hospitalisation	-0.37	-3.14	0.003	-0.34	-3.07	0.003
Type of analgesics used prior to hospitalisation (opioids *vs.* others)	0.01	0.05	0.964			
Opioid dose at hospitalisation	0.123	0.99	0.327			
VASmax for pain	-0.03	-0.25	0.807			
lnAUCβ for pain	-0.02	-0.14	0.892			
Cumulative opioid dose used during hospitalisation	0.09	0.73	0.468			

**ordinal variable, £natural logarithmic transformation of body mass index, βnatural logarithmic transformation of area under curve of VAS for pain and time, ECOG:Eastern Cooperative Oncology Group

opioids was associated with the type of current cancer treatment (chemotherapy *vs*. other treatment) (ß=-0.34, T=-2.89, *P*=0.005 and the VAS at the time of hospitalisation (ß=-0.37, T=-3.14, *P*=0.003). The multivariate model demonstrated that VAS for pain at the time of hospitalisation (ß=-0.34, T=-3.07, *P*=0.003) and the current cancer treatment regimen (chemotherapy *vs*. others) (ß=-0.31, T=-2.81, *P*=0.007) were independently associated with the outcome. These data are shown in Table 2.

Discussion

In this paper, we show for the first time that pain burden during hospitalisation is significantly and inversely associated with the risk of persistent pain. Pain burden was calculated as the AUC of the VAS-time tables, and was previously described in the literature as an associate of pain control (Gammaitoni et al., 2003; Jokela et al., 2008; Vandervaart et al., 2011). As pain burden is a function of pain intensity over time, we can conclude that any factor associated with increased pain burden would theoretically be related with diminished risk of persistent pain. In accordance, higher pain intensity scores at hospitalisation was associated with a greater benefit from opioids as we demonstrated in the subsequent analyse. The fact that patients with more severe pain were the ones who derive the greatest benefit from the opioids in our study needs to be taken into consideration when we are trying to control cancer pain. In addition, prolonged hospitalisation may mean better dose titration of opioids and better symptomatic relief, and thus may be associated with increased pain burden and diminished risk of persistent pain.

The findings of our study conflict with those of a previous study performed by Fainsinger et al. who demonstrated that patients with higher pain intensity at the initial assessment had a longer time to achieve stable pain control, required higher doses of opioids and more complicated analgesic regimens (Fainsinger et al., 2009). Similarly, our findings also conflict with those of Mercadante et al., who did not find an association between pain intensity and opioid response (Mercadante et al., 2011).

The cumulative opioid dosage and changes in the opioid dosage were associated with PPFS, most likely because patients subjected to aggressive opioid therapy exhibited good pain response. This finding is similar to that reported by Knudsen et al.(2011) who showed that pain relief is associated with opioid dosage (Knudsen et al. 2011). Changes in the VAS score while receiving the standard dosage of opioids was also associated with the type of cancer treatment; patients who were receiving chemotherapy were more likely to achieve stable pain control. Although we could not show a relationship between the PPFS and the cause of pain (bone metastasis *vs*. others), patients receiving chemotherapy were more likely to have pain control, which could indicate a clinical response and may reflect a collateral palliative benefit of chemotherapy. Apart from the factors analysed in our study, other groups have proposed additional factors

that may be associated with opioid benefit. Fainsinger et al. demonstrated in a multicentre study of the revised Edmonton Classification System for cancer-related pain that the mechanism of pain had predictive value and neuropathic pain required a longer time to achieve stable pain control (Fainsinger et al.,2005). Lower patient age and the presence of psychological distress were other predictors for (longer) time to achieve stable pain control. In addition, Kambayasi et al. identified several factors that were predictive for a higher required dosage of transdermal fentanyl . They found that breast cancer, advanced age, male sex, lower total protein and higher alanine aminotransferase levels were significant predictors of the time to achieve stable pain control (Kanbayashi et al., 2011). Liang et al. had suggested that gender may influence patients' perceptions of and responses to cancer-related pain (Liang et al., 2013). In our study, however, we did not observe any correlation between cancer type, sex, age and PPFS. Furthermore, we could not demonstrate any relationship between patient BMI and opioid efficacy, and this finding was in accordance to theirs.

In summary, the pain intensity at the time of hospitalisation, aggressiveness of opioid treatment, and usage of chemotherapy are associated with an increased benefit from opioids in cancer patients. We believe that it is important to monitor pain intensity at, during and after opioid dosage titration and to consider the predictors identified here and elsewhere in order to rapidly achieve benefits from opioid administration. More studies are required to more effectively address cancer-related pain and its palliation, especially in different parts of the world where the suboptimal treatment of cancer pain remains a problem.

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