Int J Clin Exp Med 2015;8(5):7606-7612
www.ijcem.com /ISSN:1940-5901/IJCEM0006397

Original Article

Modified glasgow prognostic score predicting high conversion ratio in opioid switching from oral oxycodone to transdermal fentanyl in patients with cancer pain

Shu-Shan Jia[1], Li Shang[2], Ming-E Li[3], Dong-Mei Zhao[4], Wen-Hua Xu[2], Yao-Qi Wang[1]

[1]Department of Anesthesiology, Affiliated Hospital of Binzhou Medical University, No. 661, Yellow-River Second Street, Binzhou 256603, People's Republic of China; [2]Department of Nursing, Affiliated Yantai Hospital of Binzhou Medical University, No. 629, Nan-Hua Street, Yantai 264000, People's Republic of China; [3]Department of Physical Examination, Affiliated Hospital of Binzhou Medical University, No. 661, Yellow-River Second Street, Binzhou 256603, People's Republic of China; [4]Department of Anatomy, Binzhou Medical University, No. 661, Yellow-River Second Street, Binzhou 256603, People's Republic of China

Received January 27, 2015; Accepted April 21, 2015; Epub May 15, 2015; Published May 30, 2015

Abstract: The aim of this study was to identify predictive factors for higher conversion ratio in opioid switching from oral oxycodone to transdermal fentanyl (TDF) in patients with cancer pain. The participants of this study were 156 hospitalized cancer patients who underwent opioid switching from oral oxycodone to TDF at the Affiliated Hospital of Binzhou Medical University between January 1st, 2010 and March 31st, 2014. Patient characteristics, modified Glasgow Prognostic Score (mGPS), daily oxycodone dose, and reasons for opioid switching were retrospectively collected. The effect of variables on the conversion ratio was analyzed by multiple regression analysis to identify the predictive factors for higher conversion ratio in opioid switching from oral oxycodone to TDF. The results showed that the mGPS (odds ratio [OR], 2.358; 95% CI 1.379-4.031; $P = 0.002$), the reason for opioid switching (OR, 0.497; 95% CI, 0.298-0.828; $P = 0.007$) and equivalent oral morphine dose (OR, 1.700; 95% CI, 1.008-2.867; $P = 0.046$) were found to be significant predictors requiring higher conversion ratio in opioid switching. This study indicates that higher mGPS, poor pain control before switching and higher equivalent oral morphine dose are significant predictors of a need for higher conversion ratio in opioid switching from oral oxycodone to TDF. These results could contribute to the establishment of evidence-based medicine in cancer pain relief.

Keywords: Transdermal fentanyl, opioid switching, oxycodone, conversion ratio, cancer pain

Introduction

Cancer is a major public health problem in the whole world and responsible for more than 0.5×10^6 deaths annually [1, 2]. The prevalence of pain in cancer patients iscrucial and even greater than 75% for those with advanced cancer [3]. Unrelieved pain impacts all dimensions of patient's quality of life and profoundly influences the patient's ability to endure treatment, to return to health as a cancer survivor, or to achieve a peaceful death. The relief of pain should be seen as part of a comprehensive pattern of cancer support care.

The transdermal fentanyl (TDF) was a synthetic opioid-receptor agonist which could provide effective, continuous pain relief in cancer pain patients [4, 5]. The fentanyl from the patch is delivered by skin permeability and by local blood flow, from which it is taken up into the systemic circulation. TDF can achieve clinically analgesia for 72 hours per patch, due to its ability of continuous release [6]. TDF has been recommended for the management of moderate to severe chronic cancer pain and general pain [7]. However, several studies have revealed that patients with poor nutritional status may decrease TDF absorption in cancer patients, which may affect clinical pain management [8-10]. In clinical practice, patients often need to switch opioid and the conversion ratios of opioid switching varied, even though a standard equivalent analgesic dose table has been provided for dose selection.

Table 1. Baseline characteristics of patients

Characteristics	All patients (n = 156)
Sex (male/female)	108/48
Age (years), median (range)	59 (37-83)
BMI, median (range)	21.4 (13.9-35.4)
CRP (mg/dL), median (range)	4.4 (0.2-76.3)
Albumin (g/dL), median (range)	37.8 (27.8-51.2)
mGPS	
0/1/2	64/61/31
Tumor metastasis	
None metastasis	83 (53.2%)
Distant metastasis	73 (46.8%)
Daily oral morphine dose	
≤ 134 mg/d	87 (55.8%)
135-224 mg/d	43 (27.6%)
≥ 225 mg/d	26 (16.6%)
Reason for opioid switching	
Adverse effect	40 (25.6%)
Poor pain control	82 (52.6%)
Unable to swallow	31 (19.9%)
Not known	3 (1.9%)
Dose-conversion Ratio	
≤ 100	83 (53.2%)
> 100	73 (46.8%)
Type of cancer	
Lung	26
Esophagus	27
Stomach	28
Colon	16
Breast	13
Pharynx	10
Liver	21
Others	15

BMI, body mass index; CRP, C-reactive protein; mGPS, modified Glasgow Prognostic Score.

The modified Glasgow prognostic score (mGPS) is based on a combination of elevated C-reactive protein (CRP) (> 10 mg/L) and hypoalbuminemia (< 35 g/L), and is indicative of both an underlying systemic inflammatory response and a nutritional decline [11]. Previous studies have reported that the mGPS was a prognostic predictor in patients with several advanced cancers [12, 13]. But reports on the relationship between mGPS and conversion ratio of opioid switching are limited. This study aimed at determining whether mGPS was associated with conversion ratio of opioid switching from oral oxycodone to TDF and examining the predicting factors for higher conversion ratio.

Materials and methods

Clinical data and patient groups

Patient care records of 156 cancer cases who were in-patients of the Affiliated Hospital of Binzhou Medical School were reviewed retrospectively between January 1st, 2010 and March 31st, 2014. These patients who were undergoing treatment for management of chronic cancer-related pain and switched from oxycodone to the TDF (Duragesic®; Janssen Pharmaceutica, Beerse, Belgium) were included in the present study. Patients who had been prescribed medication that may influence patient's pain intensity, such as anticancer drugs and analgesic adjuvants (except for nonsteroidal antiinflammatory drugs), were excluded from the analysis. All patients underwent regular follow-up at the same hospital.

Data collection

Clinical factors (sex, age, body mass index [BMI], type of cancer, laboratory tests, stage of cancer, daily dose of oral oxycodone, TDF dose) were collected. Pain intensity were retrospectively surveyed using medical records. The baseline assessment of pain was made according to the Numeric Rating Scale (NRS), with 0 indicating no pain, 10 indicating the worst pain, 1-3 indicating mild pain that did not interfere with sleep, 4-6 indicating moderate pain that interfered with sleep, and NRS scales ≥ 7 indicating severe pain with severe sleep interference [6]. The analgesic effect was considered to be stable when TDF doses were unchanged for more than or equal to 7 days after opioid switching following the method [14], and the daily TDF dose at this stable condition was judged to be adequate for pain control and used for the data analysis. The oxycodone dose before opioid switching was calculated as the corresponding morphine dose using an oxycodone to morphine conversion ratio of 2:3 [15, 16]. Patients were classified into three groups (≤ 134 mg/d; 135-224 mg/d; ≥ 225 mg/d) according to the daily equivalent oral morphine dose [14]. The oxycodone to TDF conversion ratio was calculated using daily equivalent oral morphine dose divided by the daily TDF dose [14].

To evaluate the mGPS, blood test results from the day before opioid switching (or no more

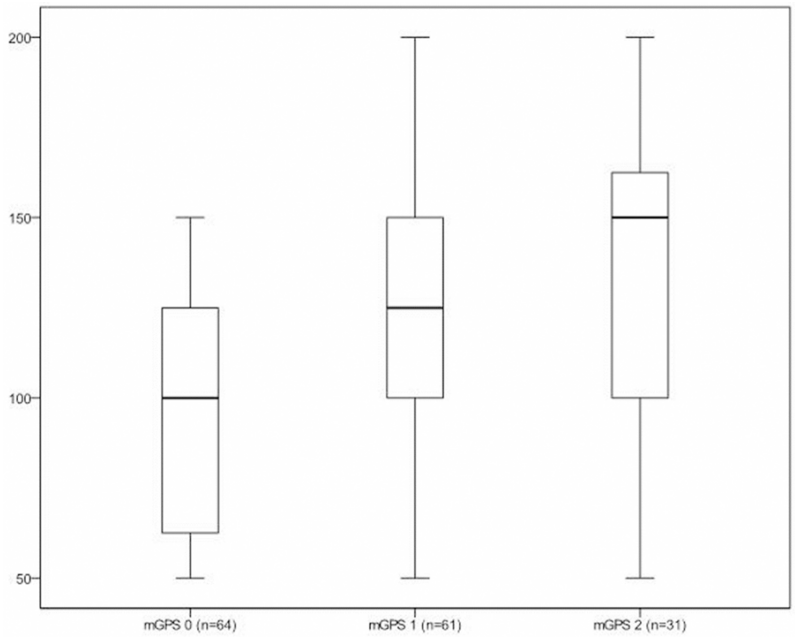

Figure 1. Box plots for the conversion ratios against mGPS 0 (n = 64), mGPS 1 (n = 61) and mGPS 2 (n = 31). Data are shown by box plot with median, 25% and 75% quartiles, and minimum and maximum values.

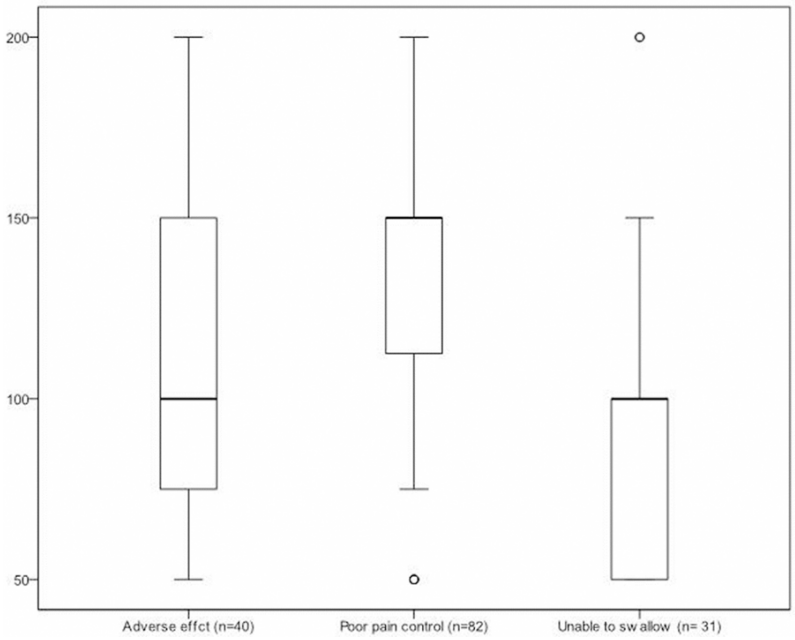

Figure 2. Box plots for the conversion ratios against reason for opioid switching. Data are shown by box plot with median, 25% and 75% quartiles, and minimum and maximum values.

than 1 week before switching) were used. The mGPS is based on both CRP and albumin. Patients who had both elevated CRP (> 10 mg/L) and hypoalbuminemia (< 35 g/L) were assigned a score of 2. Patients with only elevated CRP (> 10 mg/L) were assigned a score of 1. Patients with neither of these abnormalities were assigned a score of 0 [17].

Statistical analysis

Fisher exact test or chi-square test was used to compare categorical variables to ascertain if clinicopathologic data varied with the conversion ratios. Logistic regression models were fit for multivariate analyses to evaluate associations between conversion ratio and any of the clinical factors with $P < 0.1$ on univariate analysis. The criterion for statistical significance was set at $P < 0.05$, and p values determined from two-sided tests. All statistical analyses were performed using SPSS v16.0 (SPSS, Chicago, IL, USA).

Results

During the study period, a total of 156 patients had undergone opioid switching. Demographic and clinical data of the patients are shown in **Table 1**. There were 73 patients with distant metastasis and the lung (43/73) was the most common site of metastasis. The median CRP level was 4.4 mg/dL (ranging from 0.2 to 76.3) and the median albumin level was 37.8 g/dL (ranging from 27.8 to 51.2). There were twenty-four (15.4%) patients with BMI ≤ 18.5 kg/m^2, thirty-five (22.4%) patients with BMI between 18.5 and 20.5 kg/m^2 and ninety-seven (62.2%) patients with BMI > 20.5 kg/m^2.

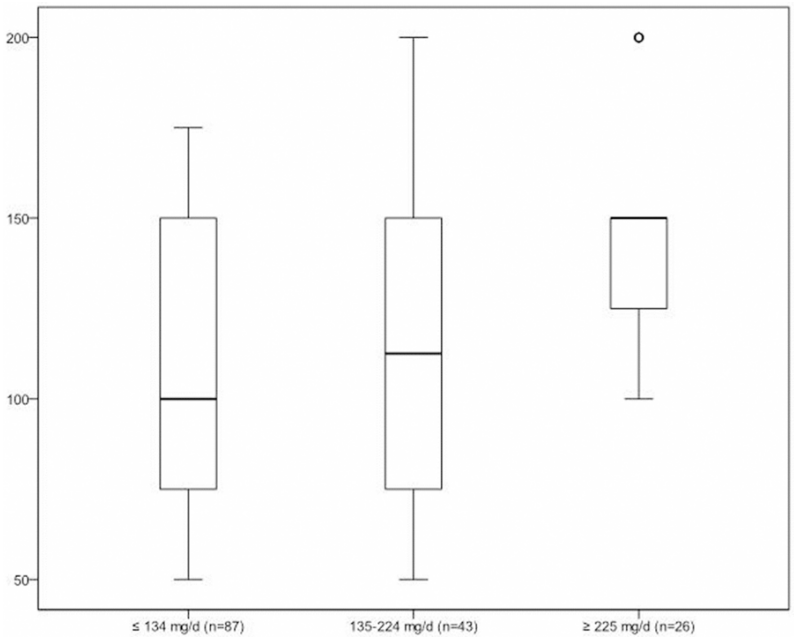

Figure 3. Box plots for conversion ratio against the daily oral morphine-equivalent oxycodone dose. Data are shown by box plot with median, 25% and 75% quartiles, and minimum and maximum values.

The box plots for the conversion ratios of each mGPS group were shown in **Figure 1**. The conversion ratio for patients with mGPS of 0 tended to be lower than that for those with mGPS of 1 and 2; the median (minimum to maximum range) conversion ratios for patients with mGPS of 0, 1, and 2 were 100 (50-150), 125 (50-200), and 150 (50-200), respectively.

The conversion ratios were classified by the reasons for opioid switching (group 1, 2, 3), and the box plots are given in **Figure 2**. The most frequent reason for opioid switching was poor pain control, which was reported in 82 (52.6%) patients (**Table 1**). The conversion ratio for patients in the poor pain control group (group 2) tended to be higher than that for those in the other groups; the median (minimum to maximum range) conversion ratios for patients in groups 1, 2, and 3 were 100 (50-200), 150 (75-200), and 100 (50-150), respectively. **Figure 3** shows the box plots for the conversion ratios of each daily equivalent oral morphine dose. The conversion ratio for group with a daily dose of ≥ 225 mg/d tended to be higher than that for the other two groups (**Figure 3**).

To determine which clinical factors were correlated with the conversion ratios, the Fisher exact test and chi-square test were used to compare categorical variables with the conversion ratios. In univariate analysis, mGPS was strongly associated with conversion ratios: 73.4% (47/64) patients with a mGPS of 0 had a conversion ratios of ≤ 100, while only 44.3% (27/61) patients with a mGPS of 1 and 29.0% (9/31) patients with a mGPS of 2 had a conversion ratios of ≤ 100 (P< 0.001, **Table 2**). The reason for opioid switching and converted oral morphine dose were also strongly associated with the conversion ratios (P < 0.001, P = 0.001; respectively). No significant difference in sex, age, BMI or tumor metastasis was found between the dose-conversion ratio group.

Clinical variables that were statistically significant (P < 0.10) in univariate analysis were analyzed further in multivariate analysis using logistic regression models. In multivariate regression analysis, mGPS (odds ratio [OR], 2.358; 95% CI 1.379-4.031; P = 0.002), the reason for opioid switching (OR, 0.497; 95% CI, 0.298-0.828; P = 0.007) and oral morphine dose (OR, 1.700; 95% CI, 1.008-2.867; P = 0.046) were found to be significant predictors requiring higher conversion ratio in opioid switching (**Table 3**).

Discussion

To our knowledge, it is the first study to explore the relationship between mGPS and conversion ratios for opioid switching from oral oxycodone to TDF. No studies on the effect of mGPS on opioid switching from oral oxycodone have been published, either. In this study, we revealed that mGPS, the reason for opioid switching and daily oral morphine dose affected the standard recommended conversion ratios for opioid switching from oral oxycodone to transdermal fentanyl. The typical conversion ratio is 100:1 (morphine to TDF) [15]. But in clinical practice, the initial conversion ratios, based on clinical studies and personal experience [15, 18], were changed to achieve the best balance between pain intensity and

Table 2. Fisher exact test or Chi-square test to determine association of dose-conversion ratio and covariates

Characteristic	Dose-conversion Ratio		*P*
	≤ 100	> 100	
Total	83 (53.2%)	73 (46.8%)	
Age (years)			0.204
≤ 60	38 (24.4%)	41 (26.3%)	
> 60	45 (28.8%)	32 (20.5%)	
Sex			0.487
Male	55 (35.3%)	53 (34.0%)	
Female	28 (17.9%)	20 (12.8%)	
BMI			0.522
> 20.5	55 (35.3%)	42 (26.9%)	
18.5-20.5	17 (10.9%)	18 (11.5%)	
≤ 18.5	11 (7.1%)	13 (8.3%)	
Tumor metastasis			0.261
non metastasis	48 (30.8%)	35 (22.4%)	
metastasis	35 (22.4%)	38 (24.4%)	
mGPS			< 0.001
0	47 (30.1%)	17 (10.9%)	
1	27 (17.3%)	34 (21.8%)	
2	9 (5.8%)	22 (14.1%)	
Reason			< 0.001
Adverse effect	22 (14.1%)	18 (11.5%)	
Poor pain control	33 (21.1%)	49 (31.4%)	
Unable to swallow	25 (16.0%)	6 (3.8%)	
Unknown	3 (1.9%)	0(0%)	
Oral morphine dose			0.001
≤ 134 mg/d	56 (35.9%)	31 (19.9%)	
135-224 mg/d	21 (13.5%)	22 (14.1%)	
≥ 225 mg/d	6 (3.8%)	20 (12.8%)	

BMI, body mass index; mGPS, modified Glasgow Prognostic Score.

Table 3. Multivariate logistic regression analysis for dose-conversion ratio

Variable	*P*	OR	95% CI for OR
mGPS	0.002	2.358	1.379-4.031
Reason	0.007	0.497	0.298-0.828
Oral morphine dose	0.046	1.700	1.008-2.867

OR, odds ratio; 95% CI, 95% confidence interval; mGPS, modified Glasgow Prognostic Score.

adverse effects. In addition, the variability in fentanyl pharmacokinetics and drug response between patients could also lead to the inter-individual variability in the conversion ratios [19, 20], which resulted in large variability of conversion ratios of opioid switching in this study.

The mGPS is based on a combination of hypoalbuminemia (< 35 g/L) and elevated CRP (> 10 mg/L), and is indicative of both an underlying systemic inflammatory response and a nutritional decline [17]. The mGPS has been reported to be a useful predictor of survival in patients with lung [21], gastrointestinal [22], and colorectal cancer [23]. In this study, a higher mGPS level could predict higher conversion ratios for opioid switching from oral oxycodone to TDF. Previous studies reported that elevated acute-phase response proteins, especially CRP, and hypoalbuminemia were associated to cancer-related cachexia [24]. Besides, the diagnostic criteria for cachexia included albumin < 35 g/L and evidence of cytokine excess (eg, elevated CRP) [25]. Heiskanen et al reported that the absorption of TDF was impaired in cachectic patients [10]. Additionally, it is also recognized that patients with cancer may have concurrent morbidity, thereby causing an increase in their CRP level and derangement of their albumin and other hematological parameters, which might influence the absorption of TDF [26]. The impaired absorption of TDF in patients with a higher level of mGPS could lead to a higher conversion ratios for opioid switching from oral oxycodone to TDF. Moreover, the concomitant nutritional decline in patients with higher level of mGPS could also reduce patient tolerance to pain and patient's compliance with analgesic treatment declines, which might also lead to a higher conversion ratios.

The reasons for opioid switching were also identified as a predictive factor. For patients with moderate-to-sever cancer pain, TDF could facilitate the continuous administration of a potent opioid, without the need for more invasive methods which involve needles and drug-infusion pumps [14]. The most frequent reason for opioid switching in the present study was the poor pain control, which was cited in 82 (52.6%) of 156 cases. Previous studies have revealed that opioid switching has been found to improve opioid responsiveness in different conditions [18, 27]. This study also revealed that the daily equivalent oral morphine dose was associated with the conversion ratios, which was in close agreement with previous reports [14].

In this study, the conversion ratios for opioid switching was not influenced by age, sex, BMI, or the tumor metastasis. The influence of age,

sex on opioid switching was still inconclusive. Mercadante et al reported that age and sex did not influence the opioid switching, which is consistent with the results in the present study [28]. Reportedly, TDF absorption is impaired to between a third and a half in patients with cachexia (mean BMI = 16 kg/m^2) [10]. But BMI of most patients was over 18.5 kg/m^2 in this study, and only 15.4% (24 of 156) had BMI < 18.5 kg/m^2 (**Table 2**). The higher BMI level in the present study suggests that any changes in TDF absorption had a minimal impact on the conversion ratio, at the time of opioid switching.

There are several potential limitations in this study, including the retrospective nature and the fact that the study was conducted in a single institution. However, we reported on a relative large study population that underwent opioid switching only from oral oxycodone to TDF. Thus, larger prospective studies will need to be carried out to confirm these preliminary results.

In conclusion, our study indicates that higher mGPS, poor pain control before switching and higher equivalent oral morphine dose are significant predictors of a need for higher conversion ratio in opioid switching from oral oxycodone to TDF. These results could contribute to the establishment of evidence-based medicine in cancer pain relief.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yao-Qi Wang, Department of Anesthesiology, Affiliated Hospital of Binzhou Medical University, No. 661, Yellow-River Second Street, Binzhou 256603, People's Republic of China. Tel: +86-543-3256544; Fax: +86-543-3256544; E-mail: wangyaoqiby@163.com

References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[2] McMillan DC. An inflammation-based prognostic score and its role in the nutrition-based management of patients with cancer. Proc Nutr Soc 2008; 67: 257-262.

[3] Paice JA and Ferrell B. The management of cancer pain. CA Cancer J Clin 2011; 61: 157-182.

[4] Grond S, Zech D, Lehmann KA, Radbruch L, Breitenbach H and Hertel D. Transdermal fentanyl in the long-term treatment of cancer pain: a prospective study of 50 patients with advanced cancer of the gastrointestinal tract or the head and neck region. Pain 1997; 69: 191-198.

[5] Menten J, Desmedt M, Lossignol D and Mullie A. Longitudinal follow-up of TTS-fentanyl use in patients with cancer-related pain: results of a compassionate-use study with special focus on elderly patients. Curr Med Res Opin 2002; 18: 488-498.

[6] Guo SP, Wu SG, Zhou J, Feng HX, Li FY, Wu YJ, Sun JY and He ZY. Transdermal fentanyl for pain due to chemoradiotherapy-induced oral mucositis in nasopharyngeal cancer patients: evaluating efficacy, safety, and improvement in quality of life. Drug Des Devel Ther 2014; 8: 497-503.

[7] Muijsers RB and Wagstaff AJ. Transdermal fentanyl: an updated review of its pharmacological properties and therapeutic efficacy in chronic cancer pain control. Drugs 2001; 61: 2289-2307.

[8] Yamamoto K, Kojima M, Iguchi H and Ohta T. [Measurement of amount of fentanyl remaining in used patches: investigation of clinical factors affecting the remaining amounts in 4 patients]. Yakugaku Zasshi 2008; 128: 959-964.

[9] Takahashi H, Chiba T, Tairabune T, Kimura Y, Wakabayashi G, Takahashi K and Kudo K. A retrospective study on the influence of nutritional status on pain management in cancer patients using the transdermal fentanyl patch. Biol Pharm Bull 2014; 37: 853-857.

[10] Heiskanen T, Matzke S, Haakana S, Gergov M, Vuori E and Kalso E. Transdermal fentanyl in cachectic cancer patients. Pain 2009; 144: 218-222.

[11] McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: a decade of experience in patients with cancer. Cancer Treat Rev 2013; 39: 534-540.

[12] Crumley AB, McMillan DC, McKernan M, McDonald AC and Stuart RC. Evaluation of an inflammation-based prognostic score in patients with inoperable gastro-oesophageal cancer. Br J Cancer 2006; 94: 637-641.

[13] McMillan DC, Crozier JE, Canna K, Angerson WJ and McArdle CS. Evaluation of an inflammation-based prognostic score (GPS) in patients undergoing resection for colon and rectal cancer. Int J Colorectal Dis 2007; 22: 881-886.

[14] Matsumura C, Yamada M, Fujihara S, Chisaki Y, Takahashi K and Yano Y. Indication of Adequate Transdermal Fentanyl Dose in Opioid

Switching From Oral Oxycodone in Patients With Cancer. Am J Hosp Palliat Care 2014; [Epub ahead of print]

[15] Caraceni A, Hanks G, Kaasa S, Bennett MI, Brunelli C, Cherny N, Dale O, De Conno F, Fallon M, Hanna M, Haugen DF, Juhl G, King S, Klepstad P, Laugsand EA, Maltoni M, Mercadante S, Nabal M, Pigni A, Radbruch L, Reid C, Sjogren P, Stone PC, Tassinari D and Zeppetella G. Use of opioid analgesics in the treatment of cancer pain: evidence-based recommendations from the EAPC. Lancet Oncol 2012; 13: e58-68.

[16] Heiskanen T and Kalso E. Controlled-release oxycodone and morphine in cancer related pain. Pain 1997; 73: 37-45.

[17] Proctor MJ, Morrison DS, Talwar D, Balmer SM, O'Reilly DS, Foulis AK, Horgan PG and McMillan DC. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. Br J Cancer 2011; 104: 726-734.

[18] Mercadante S and Bruera E. Opioid switching: a systematic and critical review. Cancer Treat Rev 2006; 32: 304-315.

[19] Gupta SK, Southam M, Gale R and Hwang SS. System functionality and physicochemical model of fentanyl transdermal system. J Pain Symptom Manage 1992; 7: S17-26.

[20] Solassol I, Bressolle F, Caumette L, Garcia F, Poujol S, Culine S and Pinguet F. Inter- and intraindividual variabilities in pharmacokinetics of fentanyl after repeated 72-hour transdermal applications in cancer pain patients. Ther Drug Monit 2005; 27: 491-498.

[21] Scott HR, McMillan DC, Forrest LM, Brown DJ, McArdle CS and Milroy R. The systemic inflammatory response, weight loss, performance status and survival in patients with inoperable non-small cell lung cancer. Br J Cancer 2002; 87: 264-267.

[22] Nozoe T, Iguchi T, Egashira A, Adachi E, Matsukuma A and Ezaki T. Significance of modified Glasgow prognostic score as a useful indicator for prognosis of patients with gastric carcinoma. Am J Surg 2011; 201: 186-191.

[23] Ishizuka M, Nagata H, Takagi K, Horie T and Kubota K. Inflammation-based prognostic score is a novel predictor of postoperative outcome in patients with colorectal cancer. Ann Surg 2007; 246: 1047-1051.

[24] Krzystek-Korpacka M, Matusiewicz M, Diakowska D, Grabowski K, Blachut K, Kustrzeba-Wojcicka I, Terlecki G and Gamian A. Acute-phase response proteins are related to cachexia and accelerated angiogenesis in gastroesophageal cancers. Clin Chem Lab Med 2008; 46: 359-364.

[25] Morley JE, Thomas DR and Wilson MM. Cachexia: pathophysiology and clinical relevance. Am J Clin Nutr 2006; 83: 735-743.

[26] Proctor MJ, Horgan PG, Talwar D, Fletcher CD, Morrison DS and McMillan DC. Optimization of the systemic inflammation-based Glasgow prognostic score: a Glasgow Inflammation Outcome Study. Cancer 2013; 119: 2325-2332.

[27] Slatkin NE. Opioid switching and rotation in primary care: implementation and clinical utility. Curr Med Res Opin 2009; 25: 2133-2150.

[28] Mercadante S, Ferrera P, Villari P, Casuccio A, Intravaia G and Mangione S. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. J Pain Symptom Manage 2009; 37: 632-641.