Overall Survival among Cancer Patients Undergoing Opioid Rotation to Methadone Compared to Other Opioids

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Abstract

Background: Methadone has been associated with lower overall survival (OS) in patients with chronic pain. There are no data available on the association of methadone with OS in cancer patients.

Objective: Our aim was to compare the OS in cancer outpatients undergoing opioid rotation (OR) to methadone and other strong opioids.

Design: Demographics, symptoms, and morphine equivalent daily dose (MEDD) were collected in patients who underwent OR from strong opioids to either methadone or other strong opioids and returned for a follow-up within six weeks.

Setting/Subjects: Nine hundred thirty-eight consecutive outpatients to the supportive care center of a tertiary cancer center were reviewed.

Measurements: Kaplan–Meier curves were used to evaluate survival.

Results: Of a total of 164 eligible patients, 54/76 patients who underwent OR to methadone and 48/88 patients who underwent OR to other opioids returned for a follow-up visit. The median age was 56 years, 54% were male, and 87% had advanced cancer. There were no significant differences between the two groups in patient characteristics, performance status, MEDD, and pain scores. The Kaplan–Meier curves revealed no significant difference in median OS between all patients undergoing OR to methadone and other opioids [3.75 months (95% confidence interval, CI, 2.30–6.46) vs. 2.62 months (95% CI 1.74–4.33); $p=0.35$] and also among those who returned for a follow-up following an OR to methadone and other opioids [5.15 months (95% CI 3.64–7.41) vs. 5.90 months (95% CI 2.62–9.28); $p=0.89$].

Conclusions: We observed no significant difference in OS in cancer patients in methadone group compared to other opioids.

Keywords: cancer pain; cancer patients; methadone; mortality; opioid rotation; survival

Introduction

METHADONE is one of the most common opioid used in cancer pain management.^{1–6} It has a unique pharmacological profile.⁴ It is extensively metabolized in the liver through cytochrome P-450 enzymes (mainly CYP3A4) and hence subjected to a large number of drug interactions.^{4,7,8} Methadone can prolong the QT interval and has been linked to fatal arrhythmias.⁸ Methadone possesses a long and variable half-life that rarely results in side effects such as excessive drowsiness and respiratory depression even 10–15 days following initiation, titration, or addition of

another drug that inhibits the CYP3A4 system.^{4,9} Methadone use has been associated with an increased mortality in patients with chronic noncancer pain.^{7,8,10,11} Yet, methadone is the most common opioid chosen for the purpose of opioid rotation (OR) from one opioid to another in cases of refractory cancer pain, opioid-induced neurotoxicity (OIN), hyperalgesia, or neuropathic pain syndromes.^{3,6,12–14} Although not fully understood, several European and North American studies report that methadone may possess a unique anti-neoplastic activity and suggested that it may be incorporated as part of a broader treatment plan for various solid tumors and also leukemia.^{15–24} Despite the prevalence of a large

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number of studies exploring the association of methadone and survival in noncancer pain patients, there are no data available on the association of methadone with overall survival (OS) in cancer patients. Our aim was to compare the characteristics and OS in cancer patients undergoing OR to methadone compared to those undergoing OR to other strong opioids.

Methods

This study represents an *ad hoc* analysis of a study previously reported by our group and was approved by the institutional review board at The University of Texas MD Anderson Cancer Center.¹²

The supportive care center (SCC) in our institute includes an interdisciplinary palliative care team that practices a standardized model of care using several validated tools.^{25,26} We retrospectively reviewed the charts of consecutive patients seen in our outpatient supportive care center in 2008 to identify patients undergoing OR from other strong opioids to methadone and from other strong opioids to another strong opioid. Data regarding demographics, patient characteristics, Edmonton Symptom Assessment System (ESAS),^{27,28} Memorial Delirium Assessment Scale (MDAS),²⁹ Cut-down, Annoyed, Guilty, Eye-opener (CAGE) questionnaire for screening for alcoholism,³⁰ pain characteristics, opioid doses, morphine equivalent daily dose (MEDD),²⁵ and survival (from tumor registry) were collected from the patient's medical record. Successful OR was defined as 2-point or 30% reduction in pain score in patients undergoing OR for uncontrolled pain, resolution of OIN in patients undergoing OR for OIN, and similarly resolution of nausea, constipation, or pruritis in patients undergoing OR for those reasons.^{12,31,32}

Statistical method

Data were summarized using standard descriptive statistics such as mean, standard deviation, and median and range for continuous variables; and frequency and proportion for cat-

egorical variables. Difference in categorical variables between two groups was examined by Chi-Squared test or Fisher's exact test when appropriate. A paired *t*-test was used to examine the change in ESAS from baseline to follow-up. Wilcoxon-Mann-Whitney test was used to compare age, MEDD, and the change of ESAS pain score between two groups. The clinical endpoint was OS time from OR, calculated as time from OR to death (event) or from OR to the last follow-up time (censored), which was estimated using the Kaplan-Meier method and the comparison between patients' characteristics groups was evaluated by log-rank test. All computations were carried out in SAS 9.3 (SAS Institute Inc., Cary, NC) and R 3.1.1.

Results

A total of 938 patients were seen in our SCC in the year 2008 and 190 patients underwent OR. Of those, 26 patients were already receiving methadone and underwent a partial OR of the breakthrough opioid only, and were excluded. Of the remaining 164 patients, 76 underwent OR from a strong opioid to methadone and 54 returned for a follow-up visit. Similarly, 88 underwent OR to another strong opioid and 48 returned for a follow-up visit (Fig. 1). There were no patients who underwent OR from methadone to another opioid. The median mg (range) of methadone used was 15 (5–105).

Table 1 shows that, of the eligible 164 patients, mean age was 56 years, 54% were male, 73% were white, and 87% had advanced cancer. CAGE score was positive in 12%, 54% had a history of smoking, and 6% had a history of drug abuse. The most common pain type was nociceptive (62%). Uncontrolled pain (79%) was the most common reason for OR followed by OIN (16%) and 69% underwent a successful OR. There were no significant differences between the methadone group and the other opioid group in patient characteristics, cancer type, advanced disease status, performance status, pain description, prerotation MEDD, baseline ESAS scores, and multiple other variables tested. Table 2 shows that there

FIG. 1. Flow chart of eligible patients.

TABLE 1. COMPARISON OF DEMOGRAPHIC AND CLINICAL CHARACTERISTICS (METHADONE GROUP VS. OTHER OPIOID GROUP)

Variables	Levels	Total, N (%)	Methadone, n (%)	Other opioid, n (%)	p
All patients		164 (100)	76 (46)	88 (54)	
Sex	Male	89 (54)	40 (53)	49 (56)	0.6958
Age	Mean $\pm$ SD	55.9 $\pm$ 13.2	54.1 $\pm$ 12.8	57.5 $\pm$ 13.3	0.0672
Race	Asian	10 (6)	7 (9)	3 (3)	0.1343
	Black	19 (12)	5 (7)	14 (16)	
	Hispanic	15 (9)	8 (10.5)	7 (8)	
	White	120 (73)	56 (74)	64 (73)	
Cancer type	Breast	12 (7)	5 (7)	7 (8)	0.4915
	Gastrointestinal	38 (23)	16 (21)	22 (25)	
	Genitourinary	13 (8)	5 (7)	8 (9)	
	Gynecologic	14 (8.5)	9 (12)	5 (6)	
	Head and neck	19 (12)	10 (13)	9 (10)	
	Lung	34 (21)	13 (17)	21 (24)	
	Sarcoma	13 (8)	9 (12)	4 (5)	
	Other	21 (13)	9 (12)	12 (14)	
Advanced disease	Yes	142 (87)	64 (84)	78 (88)	0.4069
Receiving antineoplastic treatment	Yes	102 (62)	52 (68)	50 (57)	0.1265
History of drug abuse	Yes	8 (6)	3 (5)	5 (7)	0.7191
History of smoking	Yes	88 (54)	41 (55)	47 (53)	0.8724
CAGE score	Positive	19 (12)	8 (10.5)	11 (12.5)	0.6937
Performance status	0	6 (4)	3 (4)	3 (4)	0.6957
	1	58 (40)	31 (44)	27 (36)	
	2	38 (26)	18 (26)	20 (27)	
	3	38 (26)	17 (24)	21 (28)	
	4	5 (3)	1 (1)	4 (5)	
Pain type	Mixed	32 (25)	14 (23)	18 (26.5)	0.3161
	Neuropathic	17 (13)	11 (18)	6 (9)	
	Nociceptive	81 (62)	37 (60)	44 (65)	
Reason for OR	Uncontrolled Pain	129 (79)	62 (82)	67 (77)	0.6216 ^a
	OIN	27 (16)	10 (13)	17 (19)	
	Constipation	3 (2)	2 (3)	1 (1)	
	Nausea	2 (1)	1 (1)	1 (1)	
	Other	1 (1)	0 (0)	1 (1)	
	Renal function	2 (1)	1 (1)	1 (1)	
Successful OR	Yes	70 (69)	39 (72)	31 (65)	0.4066
MEDD	Median (Q1, Q3)	134 (70, 210)	150.0 (60, 254)	121.3 (80, 200)	0.6877

CAGE, Cut-down, Annoyed, Guilty, Eye-opener questionnaire to screen for alcoholism; MEDD, morphine equivalent daily dose; OIN, opioid-induced neurotoxicity; OR, opioid rotation; SD, standard deviation.

^a*p*-Value comparing among uncontrolled Pain, OIN, and the rest.

were no significant differences between the two groups in the kinds of antineoplastic treatments received at the time of OR.

There was a significant improvement in the median ESAS pain score in both the methadone group (-2 , $p < 0.0001$) and the other opioid group (-1 , $p = 0.0034$) at the time of follow-

up after OR. However, the methadone group had a significantly higher improvement of median pain score compared to the other opioid group ($p = 0.045$).

The Kaplan–Meier curves (Fig. 2) revealed no significant difference in OS between the methadone group and the other

TABLE 2. COMPARISON OF ANTINEOPLASTIC TREATMENTS (METHADONE GROUP VS. OTHER OPIOID GROUP)

Antineoplastic treatments	Total, N (%)	Methadone, n (%)	Other opioid, n (%)	p
No current antineoplastic treatment	62 (37.8)	24 (31.6)	38 (43.2)	0.4105
Chemotherapy	38 (23.2)	22 (28.9)	16 (18.2)	
Chemotherapy and targeted therapy	15 (9.1)	6 (7.9)	9 (10.2)	
Chemotherapy and radiation	8 (4.9)	4 (5.3)	4 (4.5)	
Hormonal therapy	1 (0.6)	1 (1.3)	0 (0)	
Immunotherapy	1 (0.6)	0 (0)	1 (1.1)	
Targeted therapy	35 (21.3)	16 (21.1)	19 (21.6)	
Definitive radiation	4 (2.4)	3 (3.9)	1 (1.1)	
No current treatment	62 (37.8)	24 (31.6)	38 (43.2)	0.1265
Current antineoplastic treatment	102 (62.2)	52 (68.4)	50 (56.8)	

Overall Survival (OS): Patients undergoing opioid rotation (OR) to methadone vs. other opioids

Group A: Methadone group

Group C: Other opioid group

Overall Survival: Patients who returned for a follow-up visit after undergoing OR to methadone vs. other opioids

Group D: Methadone group

Group E: Other opioids group

E: Number of patients who died; N: Total number of patients

FIG. 2. Kaplan–Meier Survival Estimates.

opioid group [median OS: 3.75 months (95% confidence interval [CI] 2.30–6.46) vs. 2.62 months (95% CI 1.74–4.33); $p=0.35$]. Among patients who followed up after OR, the Kaplan–Meier curves did not also reveal any significant difference in the OS between the methadone group and the other opioid group [median OS: 5.15 months (95% CI 3.64–7.41) vs. 5.90 months (95% CI 2.62–9.28); $p=0.89$].

Discussion

Our study did not show any difference in OS in cancer patients receiving methadone compared to other opioids.³³ To our knowledge, this is the first study to evaluate the effect

of methadone on OS in patients with cancer. A previous report on cancer outpatients undergoing OR revealed that patients who do not follow up after an OR have a shorter OS.³⁴ In our study, there was no difference in survival in patients who returned for a follow-up after undergoing OR to methadone or other opioids.

Although not statistically significant, a higher percentage of patients achieved a successful OR to methadone than to other strong opioids. Similarly, the patients rotated to methadone experienced a statistically higher improvement in their pain score when compared to other opioids, underscoring the role of methadone as an important tool in refractory cancer pain and complex pain syndromes. Previous studies demonstrated that rotation to methadone in cancer patients was 84% successful in the outpatient setting and 77% successful in the inpatient setting, and resulted in a long-lasting improvement in pain.^{3,6,13,35,36}

Comorbidities, drug interactions, and concurrent benzodiazepine and other sedating drug use have all been identified as risk factors for increased mortality with methadone.^{7,8,37,38} An expert panel rightfully recommended extensive counseling for patients and families on methadone safety, routine use of electrocardiography monitoring of the QT interval, assessment of comorbidities and drug interactions, careful initiation and titration, and very close monitoring and follow-up in all patients being prescribed methadone for chronic pain management.⁸

Previous studies have shown that very few cancer patients report any deviations from prescribed opioid dose when educated by an interdisciplinary palliative care team,³⁹ highlighting the importance of patient and family education when prescribing methadone to cancer patients. Our group previously reported that the lower doses of methadone that are typically prescribed to closely monitored cancer patients very rarely result in significant increases in QT intervals,⁴⁰ which justifies the frequent use of methadone in cancer pain management. Guidelines for the use of methadone on the lines of those released for chronic pain patients, but stratified based on illness trajectory and prognosis are urgently needed in cancer patients receiving palliative care.

The role of methadone as an adjuvant for treating various malignancies is poorly understood. Our study did not show any therapeutic benefit of methadone on survival in cancer patients.^{15–24} However, a much larger sample size would have allowed us to determine the OS in patients undergoing OR to methadone according to different cancer types, specifically lung and breast cancers along with leukemia. Well-designed and adequately powered studies are clearly required to explore this fascinating association.

This preliminary study shows no impact of methadone use on OS in cancer patients, most of whom had advanced disease. The main limitations of this study are its retrospective design, and the patients had a variety of primary malignancies. However, it is reassuring that cancer types, stage, and performance status were not significantly different between the two groups. Our study did not report the duration of methadone used by the patients. It must be noted, however, that the vast majority of cancer patients stay on methadone and very rarely undergo OR to another opioid. Moreover, there were no patients in this study who underwent an OR from methadone to another opioid. These results must be validated in larger studies. Our team recommends the

continued use of methadone as the go-to drug for difficult-to-treat pain syndromes in diligently selected cancer patients, while participating in the usual precautions, careful monitoring, and patient education.

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Author Disclosure Statement

No competing financial interests exist.

References

1. Bruera E, Sweeney C: Methadone use in cancer patients with pain: A review. *J Palliat Med* 2002;5:127–138.
2. Leppert W: The role of methadone in cancer pain treatment—A review. *Int J Clin Pract* 2009;63:1095–1109.
3. Mercadante S: Switching methadone: A 10-year experience of 345 patients in an acute palliative care unit. *Pain Med* 2012;13:399–404.
4. Eap CB, Buclin T, Baumann P: Interindividual variability of the clinical pharmacokinetics of methadone: Implications for the treatment of opioid dependence. *Clin Pharmacokinet* 2002;41:1153–1193.
5. Trescot AM: Review of the role of opioids in cancer pain. *J Natl Compr Cancer Netw* 2010;8:1087–1094.
6. Parsons HA, de la Cruz M, El Osta B, et al.: Methadone initiation and rotation in the outpatient setting for patients with cancer pain. *Cancer* 2010;116:520–528.
7. Ray WA, Chung CP, Murray KT, et al.: Out-of-hospital mortality among patients receiving methadone for non-cancer pain. *JAMA Intern Med* 2015; 175:420–427.
8. Chou R, Cruciani RA, Fiellin DA, et al.: Methadone safety: A clinical practice guideline from the American Pain Society and College on Problems of Drug Dependence, in collaboration with the Heart Rhythm Society. *J Pain* 2014; 15:321–337.
9. Lynch ME: A review of the use of methadone for the treatment of chronic noncancer pain. *Pain Res Manag* 2005;10:133–144.
10. Buster MC, van Brussel GH, van den Brink W: An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction* 2002;97:993–1001.
11. Gagajewski A, Apple FS: Methadone-related deaths in Hennepin County, Minnesota: 1992–2002. *J Forensic Sci* 2003;48:668–671.
12. Reddy A, Yennurajalingam S, Pulivarthi K, et al.: Frequency, outcome, and predictors of success within 6 weeks of an opioid rotation among outpatients with cancer receiving strong opioids. *Oncologist* 2013;18:212–220.
13. Rhondali W, Tremellat F, Ledoux M, et al.: Methadone rotation for cancer patients with refractory pain in a palliative care unit: An observational study. *J Palliat Med* 2013; 16:1382–1387.
14. Morley JS, Bridson J, Nash TP, et al.: Low-dose methadone has an analgesic effect in neuropathic pain: A double-blind randomized controlled crossover trial. *Palliat Med* 2003;17: 576–587.
15. Friesen C, Bacher S, Hormann I, et al.: Cytotoxic effects of opioids on cancer cell lines. *Int J Clin Pharmacol Ther* 2011; 49:60–62.
16. Friesen C, Hormann I, Roscher M, et al.: Opioid receptor activation triggering downregulation of cAMP improves effectiveness of anti-cancer drugs in treatment of glioblastoma. *Cell Cycle* 2014;13:1560–1570.
17. Friesen C, Roscher M, Alt A, Miltner E: Methadone, commonly used as maintenance medication for outpatient treatment of opioid dependence, kills leukemia cells and overcomes chemoresistance. *Cancer Res* 2008;68:6059–6064.
18. Friesen C, Roscher M, Hormann I, et al.: Cell death sensitization of leukemia cells by opioid receptor activation. *Oncotarget* 2013;4:677–690.
19. Heusch WL, Maneckjee R: Effects of bombesin on methadone-induced apoptosis of human lung cancer cells. *Cancer Lett* 1999;136:177–185.
20. Maneckjee R, Minna JD: Nonconventional opioid binding sites mediate growth inhibitory effects of methadone on human lung cancer cells. *Proc Natl Acad Sci U S A* 1992;89: 1169–1173.
21. Maneckjee R, Biswas R, Vonderhaar BK: Binding of opioids to human MCF-7 breast cancer cells and their effects on growth. *Cancer Res* 1990;50:2234–2238.
22. Perez-Alvarez S, Cuenca-Lopez MD, de Mera RM, et al.: Methadone induces necrotic-like cell death in SH-SY5Y cells by an impairment of mitochondrial ATP synthesis. *Biochim Biophys Acta* 2010;1802:1036–1047.
23. Perez-Alvarez S, Iglesias-Guimaraes V, Solesio ME, et al.: Methadone induces CAD degradation and AIF-mediated necrotic-like cell death in neuroblastoma cells. *Pharmacol Res* 2011;63:352–360.
24. Singh A, Jayanthan A, Farran A, et al.: Induction of apoptosis in pediatric acute lymphoblastic leukemia (ALL) cells by the therapeutic opioid methadone and effective synergy with Bcl-2 inhibition. *Leuk Res* 2011;35: 1649–1657.
25. Dalal S, Bruera E, eds.: *The M.D. Anderson Supportive and Palliative Care Handbook. Fifth ed.* Houston, TX: The University of Texas Health Science Center at Houston, 2015.
26. Yennurajalingam S, Urbauer DL, Casper KL, et al.: Impact of a palliative care consultation team on cancer-related symptoms in advanced cancer patients referred to an outpatient supportive care clinic. *J Pain Symptom Manage* 2011;41:49–56.
27. Bruera E, Kuehn N, Miller MJ, et al.: The Edmonton Symptom Assessment System (ESAS): A simple method for the assessment of palliative care patients. *J Palliat Care* 1991;7:6–9.
28. Chang VT, Hwang SS, Feuerman M: Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000;88: 2164–2171.
29. Breitbart W, Rosenfeld B, Roth A, et al.: The Memorial Delirium Assessment Scale. *J Pain Symptom Manage* 1997;13:128–137.
30. Bush B, Shaw S, Cleary P, et al.: Screening for alcohol abuse using the CAGE questionnaire. *Am J Med* 1987;82: 231–235.
31. Reddy A, Yennurajalingam S, Reddy S, et al.: The opioid rotation ratio from transdermal fentanyl to “strong” opioids in patients with cancer pain. *J Pain Symptom Manage* 2016;51:1040–1045.
32. Reddy A, de la Cruz M, Rodriguez EM, et al.: Patterns of storage, use, and disposal of opioids among cancer outpatients. *Oncologist* 2014;19:780–785.

33. Krebs EE, Becker WC, Zerzan J, et al.: Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. *Pain* 2011;152:1789–1795.
34. Reddy A, Yennurajalingam S, de la Cruz M, et al.: Factors associated with survival after opioid rotation in cancer patients presenting to an outpatient supportive care center. *J Pain Symptom Manage* 2014;48:92–98.
35. Fredheim OM, Moksnes K, Borchgrevink PC, Skurtveit S: Opioid switching to methadone: A pharmacoepidemiological study from a national prescription database. *Palliat Med* 2012;26:804–812.
36. Mercadante S, Casuccio A, Agnello A, Barresi L: Methadone response in advanced cancer patients with pain followed at home. *J Pain Symptom Manage* 1999;18:188–192.
37. Ernst E, Bartu A, Popescu A, et al.: Methadone-related deaths in Western Australia 1993–1999. *Aust N Z J Public Health* 2002;26:364–370.
38. McCowan C, Kidd B, Fahey T: Factors associated with mortality in Scottish patients receiving methadone in primary care: Retrospective cohort study. *BMJ* 2009;338:b2225.
39. Nguyen LM, Rhondali W, De la Cruz M, et al.: Frequency and predictors of patient deviation from prescribed opioids and barriers to opioid pain management in patients with advanced cancer. *J Pain Symptom Manage* 2013;45:506–516.
40. Reddy S, Hui D, El Osta B, et al.: The effect of oral methadone on the QTc interval in advanced cancer patients: A prospective pilot study. *J Palliat Med* 2010;13:33–38.

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