Outcomes of Patients With Advanced Gastrointestinal Cancer in Relationship to Opioid Use: Findings From Eight Clinical Trials

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ABSTRACT

Background: This study assessed the patterns of opioid use among patients with advanced gastrointestinal cancers who were included in 8 clinical trials and evaluated the impact of opioid use on survival outcomes of included patients. **Methods:** Deidentified datasets from 8 clinical trials evaluating first-line systemic treatment of advanced gastrointestinal cancers were accessed from the Project Data Sphere platform (ClinicalTrials.gov identifiers: NCT01124786, NCT00844649, NCT00290966, NCT00678535, NCT00699374, NCT00272051, NCT00305188, and NCT00384176). These trials evaluated patients with pancreatic carcinoma, gastric carcinoma, hepatocellular carcinoma (HCC), and colorectal carcinoma. Multivariable logistic regression analysis was used to evaluate factors predicting the use of opioids. Kaplan-Meier survival estimates were used to compare survival outcomes in each disease entity among patients who did or did not receive opioid treatment. Multivariable Cox regression analysis was then used to further assess the impact of opioid use on survival outcomes in each disease entity. **Results:** A total of 3,441 participants were included in the current analysis. The following factors predicted a higher probability of opioid use within logistic regression analysis: younger age at diagnosis (odds ratio [OR], 0.990; 95% CI, 0.984–0.997; $P=.004$), nonwhite race (OR for white vs nonwhite, 0.749; 95% CI, 0.600–0.933; $P=.010$), higher ECOG score (OR for 1 vs 0, 1.751; 95% CI, 1.490–2.058; $P<.001$), and pancreatic primary site (OR for colorectal vs pancreatic, 0.241; 95% CI, 0.198–0.295; $P<.001$). Use of opioids was consistently associated with worse overall survival (OS) in Kaplan-Meier survival estimates of each disease entity ($P=.008$ for pancreatic cancer; $P<.001$ for gastric cancer, HCC, and colorectal cancer). In multivariable Cox regression analysis, opioid use was associated with worse OS among patients with pancreatic cancer (hazard ratio [HR], 1.245; 95% CI, 1.063–1.459; $P=.007$), gastric cancer (HR, 1.725; 95% CI, 1.403–2.122; $P<.001$), HCC (HR, 1.841; 95% CI, 1.480–2.290; $P<.001$), and colorectal cancer (HR, 1.651; 95% CI, 1.380–1.975; $P<.001$). **Conclusions:** Study findings suggest that opioid use is consistently associated with worse OS among patients with different gastrointestinal cancers. Further studies are needed to understand the underlying mechanisms of this observation and its potential implications.

J Natl Compr Canc Netw 2020;18(5):575–581
doi: 10.6004/jnccn.2019.7382

Background

Opioid analgesia is an integral part of pain management among patients with advanced cancer.^{1,2} A potential correlation between opioid analgesics and cancer progression has been previously hypothesized.^{3,4} However, most of the published data evaluating this correlation have focused on the impact of perioperative opioid anesthetics on cancer recurrence and progression.^{5,6} These studies were confounded, however, by small sample size, retrospective data collection (with the potential of missing data or bias), and little attention to patients with advanced disease who received opioids for pain management rather than as a perioperative anesthetic. To provide a better assessment of the impact of opioid use on outcomes of patients with advanced cancer, this question needs to be addressed through a prospectively collected dataset using a meticulous gathering of patient and treatment data to minimize the risk of bias and confounding factors.

Project Data Sphere is a recently launched platform that allows researchers access to deidentified clinical trial datasets.⁷ It thus represents an excellent opportunity to examine this question with limited confounders. To minimize heterogeneity of the sample used for this analysis, we focused only on patients with advanced gastrointestinal cancer. Our working hypothesis was that patients with advanced gastrointestinal cancers who received opioids have poor overall survival (OS) and progression-free survival (PFS). The aims of this study were to assess the patterns of opioid use among patients with advanced gastrointestinal cancers who were included in 8 clinical trials and to evaluate the impact of opioid use on survival outcomes of those patients.

Methods

Study Cohort

The current study represents a pooled analysis of 8 clinical trials including patients with advanced gastrointestinal

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cancers treated using first-line systemic therapy. Specifically, 2 of these trials included patients with advanced pancreatic cancer (ClinicalTrials.gov identifiers: NCT01124786, NCT00844649), 2 included patients with advanced gastric cancer (NCT00290966, NCT00678535), 1 included patients with advanced hepatocellular carcinoma (HCC; NCT00699374), and 3 included patients with advanced colorectal cancer (NCT00272051, NCT00305188, and NCT00384176). Additional details about each of these trials, including methodology and treatment arms, are provided in Table 1. For 6 of these trials, primary results were published previously.^{8–13} For the NCT01124786 study, both study arms were included, whereas for the remaining 7 studies, only active comparator arms were included.

Data Collection

For each included participant, the following data were collected (when available): age at diagnosis, body mass index (BMI), race, sex, ECOG performance status (PS), primary tumor site, number of metastatic sites, and treatment using any opioid medication. Opioid use data evaluated in the current analysis were restricted in most of the studies to opioid use concurrent with first-line systemic therapy administration. For patients in the HCC study, information about extrahepatic spread and macrovascular invasion was also included.

Endpoints

Co-primary endpoints of the current study were OS (defined as time from randomization until death of any cause) and PFS (defined as time from randomization until death or disease progression).

Statistical Analyses

Chi-square testing was initially used to compare baseline categorical variables between patients who were treated with opioids and those who were not. An independent *t* test was then used to compare baseline continuous variables between both groups. Multivariable logistic regression analysis was used to evaluate factors predicting opioid use; this model was adjusted for age at diagnosis, BMI, race, sex, ECOG PS, primary tumor site, and number of metastatic sites.

Kaplan-Meier survival estimates were then used to compare OS and PFS outcomes according to the use of any opioid for each disease entity. Multivariable Cox regression analysis was then used to evaluate factors predicting OS and PFS for each of the 4 disease entities. For patients with advanced pancreatic, gastric, or colorectal cancer, variables included in this model were age, BMI, race, sex, ECOG PS, opioid use, and number of metastatic sites. For patients with advanced HCC, variables included in this model included age, BMI, race, sex, ECOG PS, opioid use, extrahepatic spread, and

Table 1. Specifics on the 8 Clinical Trials Included in the Current Analysis

Study	Start Date	End Date	Patients Included in Current Analysis n (%)	Treatment Arms
Pancreatic cancer				
NCT01124786	May 2010	November 2012	4,430 (12.5%)	Experimental arm: gemcitabine elaidate Active comparator: gemcitabine
NCT00844649 ^a	March 2009	September 2012	367 (10.7%)	Experimental arm: gemcitabine + nab-paclitaxel Active comparator: gemcitabine
Gastric cancer				
NCT00290966 ^a	October 1998	May 2003	218 (6.3%)	Docetaxel in combination with cisplatin or docetaxel in combination with 5-FU and cisplatin vs combination cisplatin and 5-FU
NCT00678535 ^a	May 2008	March 2012	436 (12.7%)	Capecitabine in combination with cisplatin ± cetuximab
Hepatocellular carcinoma				
NCT00699374 ^a	June 2008	January 2013	544 (15.8%)	Sunitinib (experimental arm) vs sorafenib (active comparator)
Colorectal cancer				
NCT00272051 ^a	July 2002	May 2004	322 (9.4%)	Experimental arm: FOLFOX and xaliproden Control arm: FOLFOX and placebo
NCT00305188 ^a	December 2005	October 2009	434 (12.5%)	Experimental arm: FOLFOX and xaliproden Control arm: FOLFOX and placebo
NCT00384176 Horizon III ^a	August 2006	August 2015	690 (20.1%)	Experimental arm: FOLFOX and cediranib Control arm: FOLFOX and bevacizumab

^aOnly comparator arm datasets were available in the Project Data Sphere and were subsequently included in the current study cohort.

macrovascular invasion. Variables chosen in the logistic and Cox models were based on their possible correlation with opioid intake and the possible relationship to outcomes in this patient cohort.

Results

Patient Characteristics

A total of 3,441 patients were included from the 8 clinical trials: 1,277 who received an opioid medication and 2,164 who did not. Our comparison showed that patients using opioids were more likely to be nonwhite ($P<.001$), have an ECOG PS of 2 ($P<.001$), and have the pancreas as the primary tumor site ($P<.001$). No difference was found between both categories regarding age ($P=.124$), BMI ($P=.145$), or sex ($P=.490$) (Table 2). Figure 1 shows rates

Figure 1. Rates of opioid use among patients.
Abbreviation: HCC, hepatocellular carcinoma.

of opioid use among patients with different gastrointestinal cancers in the current analysis, with the highest rate seen in patients with pancreatic cancer (61.7%) and the lowest rate in those with colorectal cancer (24.6%). Mean follow-up for the study cohort was 11.42 months (SD, 7.34).

Predictors of Opioid Use

Multivariable logistic regression analysis suggested that the following factors predict a higher probability of

Table 2. Baseline Characteristics According to Opioid Use (N=3,441)

Characteristic	Opioid Use (n=1,277)	No Opioids (n=2,164)	P Value
Mean age (SD), y	59.45 (11.31)	60.07 (11.25)	.124
Mean BMI (SD), ^a kg/m ²	24.71 (4.60)	24.94 (4.41)	.145
Race			<.001
White	904 (70.8%)	1,655 (76.5%)	
Nonwhite ^b	354 (27.7)	501 (23.2%)	
Unknown	19 (1.5%)	8 (0.4%)	
Sex			.490
Male	847 (66.3%)	1,416 (65.4%)	
Female	430 (33.7%)	746 (34.5%)	
Unknown	0	2 (0.1%)	
ECOG PS ^a			<.001
0	409 (32.1%)	1,109 (51.6%)	
1	834 (65.5%)	1,014 (47.2%)	
2	31 (2.4%)	25 (1.2%)	
Primary tumor site			<.001
Pancreas	492 (38.5%)	305 (14.1%)	
Gastric	188 (14.7%)	466 (21.5%)	
Liver	242 (19%)	302 (14%)	
Colorectal	355 (27.8%)	1,091 (50.4%)	
Number of metastatic sites ^c			<.001
0	6 (0.5%)	27 (1.2%)	
1	429 (33.5%)	805 (37.2%)	
≥2	600 (47%)	1,030 (47.6%)	
Unknown	242 (19%)	302 (14%)	

Abbreviations: BMI, body mass index; HCC, hepatocellular carcinoma; PS, performance status.

^a19 patients had missing PS, and 75 patients had missing BMI.

^bIncluding black, Asian, and other non-Caucasian races.

^cNumber of metastatic sites was not available for patients with HCC. Among patients with HCC, 47 (8.6%) had evidence of macrovascular invasion and 319 (58.6%) had extrahepatic spread.

Table 3. Multivariable Logistic Regression Analysis of Factors Predicting Opioid Use

Variable	OR (95% CI)	P Value
Age (mean; SD)	0.990 (0.984–0.997)	.004
BMI (mean; SD)	1.006 (0.989–1.024)	.467
Race ^a		
Nonwhite ^b	Ref	
White	0.749 (0.600–0.933)	.010
Sex		
Male	Ref	
Female	0.936 (0.796–1.102)	.430
ECOG PS		
0	Ref	
1	1.751 (1.490–2.058)	<.001
2	2.135 (1.185–3.848)	.012
Primary tumor site		
Pancreas	Ref	
Colorectal	0.241 (0.198–0.295)	<.001
Gastric	0.249 (0.195–0.318)	<.001
Liver	0.471 (0.348–0.637)	<.001
Number of metastatic sites ^a		
1	Ref	
0	0.519 (0.207–1.300)	.162
≥2	0.963 (0.813–1.141)	.664

Abbreviations: BMI, body mass index; OR, odds ratio; PS, performance status.

^aPatients with unknown race and those with unknown number of metastatic sites were included in the analysis but are not reported in this table.

^bIncluding black, Asian, and other non-Caucasian races.

opioid use: younger age at diagnosis (odds ratio [OR], 0.990; 95% CI, 0.984–0.997; $P=.004$), nonwhite race (OR for white vs nonwhite race, 0.749; 95% CI, 0.600–0.933; $P=.010$), higher ECOG score (OR for score 1 vs score 0, 1.751; 95% CI, 1.490–2.058; $P<.001$), and pancreatic primary site (OR for colorectal vs pancreatic, 0.241; 95% CI, 0.198–0.295; $P<.001$) (Table 3).

Survival Outcomes in the Current Study

Using Kaplan-Meier survival estimates, we found that receiving opioids was consistently associated with worse OS ($P=.008$ for pancreatic cancer; $P<.001$ for gastric cancer, HCC, and colorectal cancer) (Figure 2A–D).

Opioid use was associated with worse PFS among patients with pancreatic ($P=.009$), gastric ($P=.002$), and colorectal cancers ($P=.018$), but not among those with HCC ($P=.106$) (Figure 3A–D).

Adjusted multivariable Cox regression analysis among patients with different disease entities showed that opioid use was associated with worse OS among patients with pancreatic cancer (hazard ratio [HR], 1.245; 95% CI, 1.063–1.459; $P=.007$), gastric cancer (HR, 1.725; 95% CI, 1.403–2.122; $P<.001$), HCC (HR, 1.841; 95% CI, 1.480–2.290; $P<.001$), and colorectal cancer (HR, 1.651; 95% CI, 1.380–1.975; $P<.001$). Adjusted multivariable analysis of PFS among patients with different disease

Figure 2. Overall survival according to opioid use among patients with (A) pancreatic cancer, (B) gastric cancer, (C) hepatocellular carcinoma, and (D) colorectal cancer.

Figure 3. Progression-free survival according to opioid use among patients with (A) pancreatic carcinoma, (B) gastric cancer, (C) hepatocellular carcinoma, and (D) colorectal cancer.

entities showed that opioid use was associated with worse outcomes among patients with pancreatic cancer (HR, 1.216; 95% CI, 1.043–1.416; $P=.012$) and gastric cancer (HR, 1.277; 95% CI, 1.056–1.544; $P=.012$) but not among patients with HCC (HR, 1.071; 95% CI, 0.887–1.294; $P=.475$) or colorectal cancer (HR, 1.132; 95% CI, 0.983–1.303; $P=.085$) (Table 4).

Discussion

The aim of this study was to evaluate the patterns and impact of opioid use among patients with advanced

gastrointestinal cancer recruited into 8 clinical trials. Our data suggest that opioid use is variable among patients with different gastrointestinal cancers, with those with pancreatic cancer being the most likely to use opioids. Importantly, our data show that opioid use is consistently associated with worse OS among patients with different gastrointestinal cancers.

Several possible mechanisms might explain the association between opioid use and poor survival outcomes in the current study. One possible explanation might relate to the fact that opioid analgesics have been

Table 4. Multivariable Cox Regression Analysis of Impact of Opioid Use on Survival

Disease	Overall Survival		Progression-Free Survival	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Pancreatic cancer ^a				
No opioid use	Ref		Ref	
Opioid use	1.245 (1.063–1.459)	.007	1.216 (1.043–1.416)	.012
Gastric cancer ^a				
No opioid use	Ref		Ref	
Opioid use	1.725 (1.403–2.122)	<.001	1.277 (1.056–1.544)	.012
Hepatocellular carcinoma ^b				
No opioid use	Ref		Ref	
Opioid use	1.841 (1.480–2.290)	<.001	1.071 (0.887–1.294)	.475
Colorectal cancer ^a				
No opioid use	Ref		Ref	
Opioid use	1.651 (1.380–1.975)	<.001	1.132 (0.983–1.303)	.085

Abbreviation: HR, hazard ratio.

^aAdjusted for age, race, sex, ECOG performance status, body mass index, and number of metastatic sites.

^bAdjusted for age, race, sex, ECOG performance status, body mass index, vascular invasion, and extrahepatic spread.

shown to have protumor effects in preclinical studies.¹⁴ These protumor effects have been partly linked to their inhibition of humoral and cell-mediated immunity and their proangiogenic effects.^{15,16} Along the lines of the current study, an interesting post hoc analysis of 2 randomized controlled studies evaluated the impact of methylnaltrexone (a peripherally acting μ -opioid receptor antagonist used to treat opioid-induced constipation) on the survival of patients with advanced cancer. This study has suggested that treatment using this agent (and, more so, response to this drug) is associated with improved survival.¹⁷ A second explanation might relate to the correlation between pain and poor survival outcomes among patients with different solid tumors.^{18,19} The presence of pain may be associated with more advanced local or metastatic disease, and thus poorer OS. A third explanation might be related to the fact that severe pain itself has been correlated with poor OS in patients with advanced cancer.²⁰ Opioid use might be only a surrogate marker for that severe pain. Notably, patients who used opioids in our study were more likely to have a high ECOG PS. This supports the assumption that opioid use is a culprit of poor patient-/disease-related factors rather than the real underlying reason for poorer survival.

It is also notable that opioid use has been linked to poor survival among patient populations without cancer.^{21,22} Thus, it is possible that a negative relationship between opioid use and survival does exist outside of cancer-mediated pathways.

Our study has several limitations. First, opioid use was not the primary research question in any of the

included trials. Thus, although the current study is based on a prospectively collected dataset, the research question is retrospective. Second, this pooled analysis spans 4 different cancers, and therefore there is heterogeneity in the current dataset. To mitigate the impact of this heterogeneity, survival analyses were conducted for each disease entity independently. Third, the included clinical trial datasets reported information about opioid use during first-line systemic treatment without providing detailed information about subsequent opioid use. Fourth, although the included clinical trials reported data regarding opioid use among patients with advanced gastrointestinal cancer, they did not clarify the degree or form of pain these patients experienced. Thus, it is not possible to isolate the prognostic impact of opioids from the prognostic impact of pain on survival outcomes in the studied cohort. These limitations need to be weighed against the clear strengths of the current analysis. Most important is the reliance on clinical trial datasets in generating this pooled analysis. This should indicate greater credibility of the results of the current analysis than those in previously conducted retrospective studies evaluating the same research question.

Furthermore, it is important to note that the current study evaluated patients recruited within the context of a clinical trial. Thus, included patients are more likely to have less comorbidity and better PS than the general population. Caution should therefore be exercised when generalizing the results of the current analysis to real-world settings.

Findings of the current study have several implications for clinical practice and research directions.

Although opioid analgesia can be an indispensable part of the analgesic regimen for some patients with advanced gastrointestinal cancer and intractable pain, physicians should not rush to use it in patients with milder pain symptoms that can be controlled with other pharmacologic or nonpharmacologic interventions (eg, local radiotherapy for bone metastases). Although our study suggests an association between opioid use and poorer outcomes, it falls short of establishing causation. Future research should focus on the potential mechanisms underlying opioid-induced cancer progression and whether this is universal to all opioid analgesics or pertinent only to certain subtypes; the impact of specific types/doses of opioids on oncologic outcomes in the current dataset cannot be assessed, due to the small number of patients receiving individual opioid medications.

Conclusions

Results of our study suggest that opioid use is consistently associated with worse OS among patients with different gastrointestinal cancers. Whether this results

from a genuine negative impact of opioid use on survival or opioid use serves merely as the surrogate marker for poor patient-/disease-related conditions is unclear. Further studies are needed to study the mechanisms underlying this observation.

Submitted September 26, 2019; accepted for publication November 26, 2019.

Author contributions: Study concept: All authors. Data curation and formal analysis: Abdel-Rahman. Visualization and writing—original draft: Abdel-Rahman. Writing—review and editing: All authors.

Disclosures: The authors have disclosed that they have not received any financial considerations from any person or organization to support the preparation, analysis, results, or discussion of this article.

Disclaimer: This publication is based on research using information obtained from www.projectdatasphere.org, which is maintained by Project Data Sphere, LLC. Neither Project Data Sphere, LLC, nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this publication. All procedures were performed according to the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

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