Original Study

5-Fluorouracil-related Cardiotoxicity; Findings From Five Randomized Studies of 5-Fluorouracil-based Regimens in Metastatic Colorectal Cancer

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Abstract

This pooled analysis includes de-identified patient-level datasets from 5 randomized studies. Bevacizumab- and panitumumab-containing regimens seem to be associated with a higher risk of cardiac toxicities. Bevacizumab-containing regimens seem to increase the risk of 5-fluorouracil-related ischemic events.

Background: 5-Fluorouracil (5-FU) represents the backbone of systemic therapy regimens of colorectal cancer. The current study aims at evaluating the patterns and predictors of cardiac adverse events associated with various 5-FU-based systemic therapy regimens among patients with metastatic colorectal cancer. **Materials and Methods:** This pooled analysis includes de-identified patient-level datasets from 5 randomized studies (NCT00272051, NCT00305188, NCT00115765, NCT00364013, and NCT00384176). In order to evaluate factors predicting the development of all cardiac toxicities, arrhythmias, and ischemic events, univariate logistic regression analysis was conducted. Subsequently, factors with $P < .05$ in univariate analysis were included in multivariate logistic regression analysis. **Results:** A total of 3223 patients were included in the pooled analysis. A total of 255 (7.9%) patients developed some form of a cardiac toxicity, among which 153 (4.7%) patients developed some form of arrhythmia and 62 (1.9%) patients developed an ischemic event. Within multivariate logistic regression analysis for factors predicting cardiac toxicities, only bevacizumab-containing regimens ($P = .002$) and panitumumab-containing regimens ($P < .001$) were predictive for the occurrence of cardiac toxicity. Similarly, within multivariate logistic regression analysis for factors predicting cardiac arrhythmias, only panitumumab-based regimens were predictive of the occurrence of arrhythmias ($P < .001$). Likewise, within multivariate logistic regression analysis for factors predicting cardiac ischemia, only bevacizumab-containing regimens were predictive of ischemic events ($P = .004$). **Conclusions:** Bevacizumab- and panitumumab-containing regimens seem to be associated with a higher risk of cardiac toxicities compared with other 5-FU-based regimens. Bevacizumab-containing regimens seem to increase the risk of 5-FU-related ischemic events, whereas panitumumab-containing regimens seem to increase the risk of arrhythmias.

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Introduction

5-Fluorouracil (5-FU) represents the backbone of systemic therapy regimens of colorectal cancer (CRC), both in the adjuvant and metastatic settings.[1] In addition to the common toxicities of 5-FU (like diarrhea and skin toxicities), cardiac toxicity stands out as a serious, albeit uncommon, side effect of 5-FU-based chemotherapy.[2] The most notorious cardiac toxicities associated with 5-FU include coronary vasospasm, coronary thrombosis, and sudden cardiac death.[3]

Previous studies evaluating the patterns of 5-FU-related cardiotoxicity were mostly based on retrospective institution- or population-based registries.[4] Moreover, the cardiotoxicity of newer 5-FU-based regimens combining targeted therapies with chemotherapy was not adequately assessed.[5] Additionally, in many of these studies, the baseline cardiac status of included patients is not clear.[6]

Thus, there is a need to thoroughly assess the patterns of cardiac events among 5-FU-treated patients based on credible prospectively collected datasets that incorporate chemotherapy/targeted therapy combinations. It is also important to ensure that the baseline cardiac

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Table 1 Cohorts Included in the Pooled Analysis

Study	Treatment Regimen	Patients in the Pooled Analysis, %	Start Date	Completion Date
NCT00272051 (comparator arm only)[a]	Active comparator: placebo plus FOLFOX chemotherapy	10	July 2002	May 2004
NCT00305188 (comparator arm only)[a]	Active comparator: placebo plus FOLFOX chemotherapy	13.5	December 2005	October 2009
NCT00115765 (PACCE)	Experimental arm: chemotherapy and bevacizumab with panitumumab. Active comparator: chemotherapy and bevacizumab.	26.1	June 2005	December 2009
(NCT00364013) (PRIME)	Experimental arm: panitumumab plus FOLFOX Active comparator: FOLFOX alone	29	August 2006	March 2013
NCT00384176 (Horizon III) (comparator arm only)[a]	Active comparator: bevacizumab plus FOLFOX.	21.4	August 2006	August 2015

Abbreviations: FOLFOX = 5-FU, leucovorin, and oxaliplatin; PACCE = Panitumumab Advanced Colorectal Cancer Evaluation Study; PRIME = Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy.
[a]In these 3 studies, only comparator arms were included.

status of included patients is well-known. The best vignette to fulfill the above requirements is a secondary analysis of clinical trial datasets.

Project Data Sphere (PDS) represents an important initiative from a number of stakeholders who are interested in sharing of de-identified clinical trial datasets.[7] Within this portal, a number of clinical trials evaluating different 5-FU-based regimens in the first-line treatment of metastatic CRC are present. A secondary analysis of these clinical trials was deemed a credible way to answer the above research question.

Given the position of CRC as one of the most common cancers as well as one of the leading causes of cancer mortality worldwide, and given the widespread use of 5-FU-based regimens in both adjuvant and metastatic settings of this disease, results of the current analysis should hopefully inform practicing physicians and help patients.[8,9]

The aim of the current study is to evaluate the patterns and predictors of cardiac adverse events associated with various 5-FU-based systemic therapy regimens among patients with metastatic CRC.

Materials and Methods

Data Sources

The primary data sources for the current study include de-identified datasets from 5 randomized studies (NCT00272051, NCT00305188, NCT00115765, NCT00364013, and NCT00384176). These studies evaluated different systemic therapy regimens in the setting of first-line treatment of metastatic CRC. These de-identified datasets were obtained from the PDS platform after having relevant approvals. Informed consent was obtained from all included participants in all included studies. Primary methodological considerations and eligibility criteria were detailed in the clinicaltrials.gov records of each study. Primary results were published elsewhere for the following 3 trials: NCT00115765, NCT00364013, and NCT00384176.[10-12]

Different 5-FU-based Regimens Evaluated in the Current Pooled Analysis

The first 2 trials evaluated the impact of xaliproden in the reduction (NCT00272051) or prevention (NCT00305188) of oxaliplatin-related neuropathy among patients with metastatic CRC receiving first-line FOLFOX (5-FU, leucovorin, and oxaliplatin) chemotherapy. Another trial (NCT00364013) evaluated the impact of panitumumab addition on the outcomes of patients with metastatic CRC receiving first-line FOLFOX chemotherapy. Another trial (NCT00115765) evaluated the impact of panitumumab addition on the outcomes of patients with metastatic CRC receiving first-line chemotherapy/bevacizumab combination. The last trial (NCT00384176) evaluated a cediranib/FOLFOX combination regimen versus a bevacizumab/FOLFOX combination regimen.

For 3 of the included trials (NCT00272051, NCT00305188, and NCT00384176), only control arm datasets were available in the PDS platform, and they were included in the pooled analysis. For the other 2 studies (NCT00115765 and NCT00364013), both experimental and control arms were available in the PDS platform, and they were included in the pooled analysis. Table 1 provides a summary of the different cohorts included in the current pooled analysis.

Data Collection

Where available, the following data were collected from each of the included datasets: age at diagnosis, gender, race, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumor location, number of sites with metastatic disease, chemotherapy regimen, diabetes mellitus, and hypertension. Incidence, grade, and time to start of all cardiac toxicities and specifically of arrhythmias and ischemic episodes were also collected. Cardiac toxicities were graded in different studies according to Common Terminology Criteria of Adverse Events.

According to the available protocols of all included studies, all participants have adequate organ function (including liver, renal, bone marrow, and cardiac function) in addition to satisfactory performance status. Patients with prior clinically significant cardiac disease (including arrhythmias and cardiac ischemia) were excluded.

Statistical Analysis

Descriptive statistics were first conducted (including frequencies and percentages) of different baseline characteristics. The χ^2 test was also used to examine the differences in frequencies of cardiac adverse events according to the type of chemotherapy regimen.

Table 2 Baseline Characteristics of Included Patients in the Cohort (3223 Patients)

Parameter	N (%)
Age, y	
Mean (SD)	60.7 (11.06)
Missing	0
Gender	
Male	1925 (59.7)
Female	1298 (40.3)
Race	
Caucasian	2925 (90.8)
Others	292 (9.1)
Unknown	6 (0.2)
BMI	
Mean (SD)	26.29 (5.05)
Missing	65
ECOG	
0	1848 (57.3)
1	1295 (40.2)
2	66 (2)
Missing	14 (0.5)
Primary tumor site	
Colon	1726 (53.5)
Rectum	807 (25)
Unknown	690 (21.4)
Number of organs with distant metastases	
1	977 (30.3)
$\geq$ 2	1552 (48.2)
Unknown	694 (21.5)
Panitumumab-containing chemotherapy	
Yes	889 (27.6)
No	2334 (72.4)
Bevacizumab-containing chemotherapy	
Yes	1574 (48.8)
No	1649 (51.2)
Diabetes mellitus	
Yes	267 (8.3)
No	2021 (62.7)
Unknown	935 (29)
Hypertension	
Yes	817 (25.3)
No	1471 (45.6)
Unknown	935 (29)
Any cardiac toxicity	
Yes	255 (7.9)
No	2968 (92.1)
Arrhythmia	
Yes	153 (4.7)
No	3070 (95.3)
Ischemic attacks	
Yes	62 (1.9)
No	3161 (98.1)

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group performance status; SD = standard deviation.

To evaluate factors predicting the development of all cardiac toxicities; arrhythmias and ischemic events, univariate logistic regression analysis was conducted. Subsequently, factors with $P < .05$ in univariate analysis were included in multivariate logistic regression analysis. SPSS statistical software (IBM, Armonk, NY) version 20.0 was used in all statistical procedures.

Results

Patient Characteristics

A total of 3223 patients were included in the pooled analysis. The mean age at diagnosis was 60.7 years (SD, 11.06 years), and the mean body mass index was 26.29 (SD, 5.05). Of the participants, 59.7% were men, 90.8% were of Caucasian race, and 57.3% had an ECOG score of 0. Other baseline characteristics, including primary tumor site, number of sites with metastases, and chemotherapy regimens, are illustrated in Table 2.

Details of Cardiac Toxicities

A total of 255 (7.9%) patients developed some form of a cardiac toxicity, among which 153 (4.7%) patients developed some form of arrhythmia and 62 (1.9%) patients developed an ischemic event. The remaining 40 patients developed non-specified forms of cardiac adverse events.

Comparing bevacizumab-based regimens with non-bevacizumab based regimens, bevacizumab-based regimens were more likely to be associated with any cardiac toxicity (9.8% vs. 6.1%; $P < .001$) and ischemic events (2.9% vs. 1%; $P < .001$); but not arrhythmias (5.4% vs. 4.1%; $P = .088$). More specifically, the absolute number of ischemic events among patients receiving bevacizumab-containing regimens is 46 patients, and the absolute number of ischemic events among non−bevacizumab-containing regimens is 16 patients. Likewise, comparing panitumumab-based regimens with non−panitumumab-based regimens, panitumumab-based regimens were more likely to be associated with any cardiac toxicity (11.5% vs. 6.6%; $P < .001$) and arrhythmias (7.5% vs. 3.7%; $P < .001$), but not ischemic events (1.8% vs. 2%; $P = .752$).

Arrhythmias were graded as grade 1 in 74 patients, grade 2 in 43 patients, grade 3 in 24 patients, grade 4 in 3 patients, and grade 5 (fatal) in 9 patients. The median time to develop arrhythmia was 15 days. Among patients who developed arrhythmias, 33 patients developed atrial fibrillation, 3 patients developed atrial flutter, 7 patients developed supraventricular tachycardia, 5 patients developed ventricular arrhythmia, and 48 patients developed unspecified tachycardia. Two patients developed atrioventricular/bundle branch block, 4 patients developed sinus bradycardia, and 10 patients developed unspecified bradycardia. The remaining 41 patients developed non-specified forms of arrhythmias.

Ischemic events were graded as grade 1 in 18 patients, grade 2 in 17 patients, grade 3 in 12 patients, grade 4 in 11 patients, and grade 5 (fatal) in 4 patients. The median time to develop an ischemic

Table 3 Multivariate Logistic Regression Analysis for Factors Predicting Any Cardiac Toxicity

Parameters	Odds Ratio (95% CI)	*P* Value
Age (continuous)	1.011 (0.999-1.023)	.085
Pre-existing hypertension		
Yes	Reference	
No	0.752 (0.549-1.030)	.076
Concurrent panitumumab treatment		
Yes	Reference	
No	0.574 (0.431-0.765)	.002
Concurrent bevacizumab treatment		
Yes	Reference	
No	0.522 (0.348-0.784)	< .001

Abbreviations: CI = confidence interval; HR = hazard ratio.

event was 74 days. Among patients who developed ischemic events, 37 patients had an attack of angina, 11 patients had a myocardial infarction, and the remaining 14 patients had non-specified forms of ischemic heart disease.

Predictors of Cardiac Toxicity

The following factors were evaluated in univariate logistic regression analysis as potential predictors of any cardiac toxicity: age at diagnosis, gender, race, body mass index, ECOG score, pre-existing diabetes mellitus, pre-existing hypertension, bevacizumab-containing regimens, and panitumumab-containing regimens. Among these factors, only age, pre-existing hypertension, bevacizumab-containing regimens, and panitumumab-containing regimens were predictive of cardiac toxicity ($P < .05$). When these 4 factors were enrolled in multivariate logistic regression model, only bevacizumab-containing regimens ($P = .002$) and panitumumab-containing regimens ($P < .001$) were predictive for the occurrence of cardiac toxicity (Table 3).

A similar set of factors were evaluated in univariate logistic regression analysis as predictors of arrhythmias, and among these factors only body mass index, pre-existing hypertension, and panitumumab-containing regimens were predictive of arrhythmias ($P < .05$). When these factors were included into a multivariate logistic regression model, only panitumumab-containing regimens were predictive of the occurrence of arrhythmias ($P < .001$) (Table 4).

Likewise, the same set of factors was evaluated in univariate logistic regression analysis as predictors of ischemic events. Among these factors, only age, pre-existing hypertension, and bevacizumab-containing regimens were predictive of ischemic events ($P < .05$). When these factors were included in multivariate logistic regression analysis, only bevacizumab-containing regimens were predictive of ischemic events ($P = .004$) (Table 5).

Additionally, ischemic events were classified into early events (starting < 15 days) and delayed events (starting ≥ 15 days). Fifteen early ischemic events were reported, whereas 47 delayed ischemic events were reported in the current study. Within the early events, 12 events were reported among patients receiving bevacizumab-containing regimens, and 3 events were reported among patients receiving patients receiving non−bevacizumab-containing regimens. With additional univariate logistic regression analysis, bevacizumab-containing regimens were predictive of both early and delayed ischemic events ($P = .026$ and $P = .002$, respectively).

Discussion

The current study provides an analysis of the patterns and predictors of cardiac toxicities among patients with metastatic CRC receiving a number of different first-line 5-FU-based chemotherapy regimens. Generally, bevacizumab- and panitumumab-containing regimens seem to be associated with a higher risk of cardiac toxicities compared with other 5-FU-based regimens. More specifically,

Table 4 Multivariate Logistic Regression Analysis for Factors Predicting Arrhythmias

Parameters	Odds Ratio (95% CI)	*P* Value
BMI (continuous)	1.022 (0.990-1.054)	.175
Pre-existing hypertension		
Yes	Reference	
No	0.732 (0.488-1.099)	.133
Concurrent panitumumab treatment		
Yes	Reference	
No	0.463 (0.326-0.659)	< .001

Abbreviations: BMI = body mass index; CI = confidence interval; HR = hazard ratio.

Table 5 Multivariate Logistic Regression Analysis for Factors Predicting Ischemic Episodes

Parameters	Odds Ratio (95% CI)	*P* Value
Age (continuous)	1.023 (0.998-1.049)	.066
Pre-existing hypertension		
Yes	Reference	
No	0.616 (0.349-1.086)	.094
Concurrent bevacizumab treatment		
Yes	Reference	
No	0.287 (0.122-0.676)	.004

Abbreviations: CI = confidence interval; HR = hazard ratio.

bevacizumab-containing regimens seem to increase the risk of 5FU-related ischemic events, whereas panitumumab-containing regimens seem to increase the risk of arrhythmias.

A number of pathologic mechanisms were hypothesized to explain the development of 5-FU cardiotoxicity. These include arterial endothelial damage, followed by platelet aggregation, arterial vasoconstriction, and myocardial inflammation.[13] Bevacizumab (like many other antiangiogenic agents) is well-known to predispose to thromboembolic complications.[14] Thus, the increased risk of ischemic events with bevacizumab-containing regimens is expected. Likewise, panitumumab is well-known to predispose to electrolyte disturbances (especially hypomagnesemia).[15] This might partly explain the increased risk of cardiac arrhythmias with panitumumab-containing regimens.

The current study contains a number of limitations that have to be recognized. First, the issue of cardiac toxicity was not the primary research question of any of the included studies. Thus, although the current analysis is based on prospectively collected datasets, it essentially represents a retrospective analysis of these prospectively collected datasets with all the expected shortcomings of a retrospective analysis. Second, because of the heterogeneity of data collection practices as well as the protocol of each study, some baseline information was missing. These limitations need to be weighed against the obvious strengths of the current analysis; most importantly, the reliance on well-controlled prospectively collected information, which would provide a higher credibility compared with previous reports of 5-FU-related cardiotoxicity. Moreover, because patients with a history of serious clinical illness (including cardiac events) were excluded from inclusion into these studies, the establishment of an association with treatment regimens seems to be more credible.

It has also to be noted that given the highly selective context of patients included within clinical trials (ie, younger age, good performance status, and minimal comorbidity), it is expected that rates and severity of cardiac toxicity would be quite higher in real-life settings compared with the findings of the current analysis. Thus, extra caution should be exercised when administering these regimens in routine practice settings.

A number of research questions need to be answered in future studies, including the safety of 5-FU re-challenge after a previous 5-FU-associated cardiac event and the feasibility of using another fluoropyrimidine (eg, capecitabine, S-1, or TAS-01) following a 5-FU-associated cardiac event. Moreover, among patients with recent cardiac events (eg, unstable angina or supraventricular arrhythmia), it is important to determine if there is a safe "washout period," following which fluoropyrimidines can be used. It is notable that many clinical trials used 1 year as the potential "washout period" between cardiac events and the use of 5-FU. However, this seems more to be an empirical estimate, and more formal assessment of this topic is needed.

In conclusion, bevacizumab- and panitumumab-containing regimens seem to be associated with a higher risk of cardiac toxicities compared with other 5-FU-based regimens. Bevacizumab-containing regimens seem to increase the risk of 5-FU-related ischemic events, whereas panitumumab-containing regimens seem to increase the risk of arrhythmias. Practicing oncologists should pay a specific attention to cardiac toxicities among patients treated with any of these regimens.

Clinical Practice Points

- This pooled analysis includes de-identified patient-level datasets from 5 randomized studies (NCT00272051, NCT00305188, NCT00115765, NCT00364013, and NCT00384176).
- To evaluate factors predicting the development of all cardiac toxicities, arrhythmias, and ischemic events, univariate logistic regression analysis was conducted.
- Subsequently, factors with $P < .05$ in univariate analysis were included in multivariate logistic regression analysis.
- A total of 3223 patients were included in the pooled analysis.
- A total of 255 (7.9%) patients developed some form of a cardiac toxicity, among which 153 (4.7%) patients developed some form of arrhythmia and 62 (1.9%) patients developed an ischemic event.
- Within multivariate logistic regression analysis for factors predicting cardiac toxicities, only bevacizumab-containing regimens ($P = .002$) and panitumumab-containing regimens ($P < .001$) were predictive for the occurrence of cardiac toxicity.
- Similarly, within multivariate logistic regression analysis for factors predicting cardiac arrhythmias, only panitumumab-based regimens were predictive of the occurrence of arrhythmias ($P < .001$).
- Likewise, within multivariate logistic regression analysis for factors predicting cardiac ischemia, only bevacizumab-containing regimens were predictive of ischemic events ($P = .004$).

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Disclosure

The authors have stated that they have no conflicts of interest.

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