International Journal of Colorectal Disease (2019) 34:675–680
https://doi.org/10.1007/s00384-019-03252-y

ORIGINAL ARTICLE

Predictors of toxicity-related hospitalization in four randomized studies of 5-fluorouracil-based chemotherapy in metastatic colorectal cancer

Omar Abdel-Rahman[1,2] · Osama Ahmed[3]

Accepted: 18 January 2019 / Published online: 24 January 2019

Abstract

Objective To evaluate the predictors of toxicity-related hospitalization associated with various chemotherapy regimens among metastatic colorectal cancer patients

Methods This pooled analysis includes patient-level datasets from four randomized clinical studies (NCT00272051; NCT00305188; NCT00115765; NCT00364013). Through univariate and multivariate logistic regression analyses, factors predicting the development of serious adverse events, fatal adverse events, and toxicity-related hospitalizations were determined.

Results A total of 2533 patients were included in the current study. A total of 1010 patients (39.9%) experienced one or more episodes of serious adverse events. These include 914 patients (36.1%) who were hospitalized at least once and 148 patients (5.8%) who suffered from a fatal adverse event. Within multivariate logistic regression analysis, older age ($P < 0.001$), higher ECOG score ($P < 0.001$), bevacizumab-containing chemotherapy ($P < 0.001$), and panitumumab-containing chemotherapy ($P < 0.001$) were predictive of hospitalization. Similarly, older age ($P < 0.001$), higher ECOG score ($P < 0.001$), and panitumumab-containing chemotherapy ($P = 0.003$) were predictive of fatal adverse events in multivariate logistic regression analysis. Moreover, in a multivariate Cox regression analysis, hospitalization was predictive of worse overall survival ($P < 0.001$) and progression-free survival ($P < 0.001$).

Conclusions Older age, poorer performance status, and bevacizumab- and panitumumab-containing regimens are associated with a higher risk of hospitalization. Moreover, hospitalization is predictive of worse overall and progression-free survival.

Keywords 5-fluorouracil · Serious adverse events · Fatal adverse events · Hospitalization · Colorectal cancer

Introduction

The development of serious adverse events and subsequent hospitalization in the context of systemic therapy for colorectal cancer is a big concern for patients and physicians alike [1]. Moreover, it carries significant cost implications for the health care system [2].

Previous studies assessing the patterns and predictors of hospitalization among colorectal cancer patients were based on registry databases or retrospective institutional studies that combine early and metastatic cases together and that did not differentiate between hospital admissions because of toxicities or hospital admissions because of other reasons [3]. Moreover, there was no clear correlation between patient or treatment characteristics and rates of hospitalization. Additionally, baseline performance and comorbidity information were mostly unknown in these studies and the types of chemotherapy regimens used in these studies were outdated by today's standards [4, 5].

Thus, in order to provide a more credible and up-to-date assessment of the predictors of hospitalization, there is a need to answer this research question based on prospective datasets (dedicated for metastatic colorectal cancer patients) which provide sufficient information about baseline performance and comorbidity as well as differentiate toxicity-related hospital admissions from other vignettes of hospital admissions.

✉ Omar Abdel-Rahman
omar.abdelsalam@ahs.ca

[1] Clinical Oncology Department, Faculty of Medicine, Ain Shams University, Cairo, Egypt

[2] Department of Oncology, Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta T2N4N1, Canada

[3] Department of Oncology, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

Table 1 Cohorts included in the pooled analysis

Study	Treatment regimen	Percentage of patients in the pooled analysis (%)	Start date	Completion date
(NCT00272051) (Comparator arm only)[a]	Active comparator: Placebo plus FOLFOX chemotherapy	12.7	July 2002	May 2004
(NCT00305188) (comparator arm only)[a]	Active comparator: Placebo plus FOLFOX chemotherapy	17.1	December 2005	October 2009
(NCT00115765) (PACCE)	Experimental arm: chemotherapy and bevacizumab With panitumumab Active comparator: chemotherapy and bevacizumab	33.3	June 2005	December 2009
(NCT00364013) (PRIME)	Experimental arm: panitumumab plus FOLFOX Active comparator: FOLFOX alone	36.9	August 2006	March 2013

[a] In these three studies, only comparator arms were included

The use of de-identified clinical trial datasets seems to provide a suitable medium to answer the above research question and it fulfills all the criteria outlined above. Project Data Sphere (PDS) is one of a number of recent platforms which provide access to these datasets [6], and it was utilized in the context of the current study.

The status of colorectal cancer as a leading cause of mortality and morbidity in cancer patients and widespread use of systemic chemotherapy in the treatment of advanced stages of the disease give additional weight to the current analysis and indicate its importance to patients and practicing physicians alike [7, 8].

The current study aims to evaluate the predictors of serious adverse events (and hospitalization in particular) associated with various chemotherapy regimens among metastatic colorectal cancer patients.

Methods

Data sources

The primary sources of data for the current study include de-identified datasets from four randomized studies (NCT00272051; NCT00305188; NCT00115765; NCT00364013) which were downloaded from the PDS platform after relevant approvals. Details of the included studies are summarized in Table 1. Detailed methodology and eligibility criteria were illustrated in the clinicaltrials.gov records of each study. Primary results were published elsewhere for the following two trials (NCT00115765; NCT00364013) [9, 10].

For two of the included studies (NCT00272051; NCT00305188), control arm datasets only were available in the PDS database; while for the other two studies (NCT00115765; NCT00364013), datasets of both treatment arms were available in the PDS database and they were included in the current study (Table 1).

Data collection

The following data were collected, where available, from the included datasets: age at diagnosis; race; gender; ECOG performance status; body mass index; primary tumor location; number of sites with metastatic disease; type of chemotherapy; concurrent diabetes mellitus; and hypertension. A serious adverse event is defined in each of the included studies according to the FDA definition [11]. The incidence of serious adverse events, fatal adverse events, and toxicity-related hospitalizations were recorded in each of the included datasets. Detailed toxicities which lead to hospitalization were also recorded.

Statistical analysis

Frequencies and percentages of different baseline characteristics were first detailed in descriptive statistics. Chi-squared test was also employed to evaluate the differences in baseline characteristics between patients who were or were not hospitalized because of toxicity.

In order to determine factors predicting the development of serious adverse events; fatal adverse events; and hospitalization, univariate and multivariate logistic regression analyses were conducted (factors with $P < 0.05$ in the univariate analysis were included in the multivariate logistic regression analysis). The impact of hospitalization on overall and progression-free survival was further assessed in the univariate and multivariate Cox regression analyses. Factors with $P < 0.05$ in the univariate Cox regression analysis were included in multivariate Cox regression analyses. SPSS statistical software (IBM; NY) version 20.0 was used in all statistical procedures.

Results

Patients characteristics

A total of 2533 patients were included in the current study. Mean age at diagnosis was 61.05 years (SD, 11.12) and mean body mass index was 26.38 (SD, 5.01). 90.1% of the participants were of the Caucasian race, 60.2% of the participants were men, and 57.8% have an ECOG score of 0. Additional characteristics (including the number of sites with distant metastases, primary tumor site, prior surgery, and chemotherapy treatments) were clarified in Table 2.

A total of 1010 patients (39.9%) experienced one or more episodes of serious adverse events. These include 914 patients (36.1%) who were hospitalized at least once and 148 patients (5.8%) who suffered from a fatal adverse event. Among patients who had fatal adverse events, 110 patients were hospitalized before death. Causes of hospitalization included hematological disorders in 7% of cases, cardiac causes in 3% of cases, gastrointestinal causes in 29% of cases, infections in 13% of cases, neurological disorders in 3% of cases, respiratory disorders in 7% of cases, renal disorders in 3% of cases, general/ administration site disorders in 9% of cases, nutritional disorders in 9% of cases, and other disorders in 17% of cases. Mean follow-up was 19.11 (SD, 11.67).

Comparing patients who were hospitalized versus those who were not hospitalized, patients who were hospitalized were more likely to have older age ($P < 0.001$), higher ECOG score ($P < 0.001$), less likely to have prior surgery ($P < 0.001$), more likely to be treated with bevacizumab-containing chemotherapy ($P < 0.001$) or panitumumab-containing chemotherapy ($P < 0.001$), and more likely to have pre-existing hypertension ($P = 0.002$). There was no difference between both groups with regard to race, gender or primary tumor site, number of organs with distant metastases, or pre-existing diabetes mellitus.

Table 2 Baseline characteristics of included patients in the cohort (2533 patients)

Parameter	Number (%)
Age	
Mean (SD)	61.05 (11.12)
Missing	0
Gender	
Male	1525 (60.2%)
Female	1008 (39.8%)
Race	
Caucasian	2281 (90.1%)
Others	252 (9.9%)
Body mass index	
Mean (SD)	26.38 (5.01)
Missing	15
ECOG	
0	1464 (57.8%)
1	1001 (39.5%)
2	65 (2.6%)
Missing	3 (0.1%)
Primary tumor site	
Colon	1726 (68.1%)
Rectum	807 (31.9%)
Number of organs with distant metastases	
1	977 (38.6%)
≥ 2	1552 (61.3%)
Unknown	4 (0.2%)
Prior surgery to the primary	
Yes	1205 (47.6%)
No	1328 (52.4%)
Panitumumab-containing chemotherapy	
Yes	889 (35.1%)
No	1644 (64.9%)
Bevacizumab-containing chemotherapy	
Yes	884 (34.9%)
No	1649 (65.1%)
Diabetes mellitus	
Yes	185 (7.3%)
No	1413 (55.8%)
Unknown	935 (36.9%)
Hypertension	
Yes	592 (23.4%)
No	1006 (39.7%)
Unknown	935 (36.9%)
SAEs	
Yes	1010 (39.9%)
No	1523 (60.1%)
Hospitalization	
Yes	914 (36.1%)
No	1619 (63.9%)
FAEs	
Yes	148 (5.8%)
No	2385 (94.2%)

BMI, body mass index; *SD*, standard deviation; *SAE*, serious adverse event; *FAE*, fatal adverse event

Predictors of serious adverse events and hospitalization

The following parameters were assessed in the univariate logistic regression analysis as possible predictors of serious adverse events: race, gender, age at diagnosis, ECOG score, body mass index; pre-existing diabetes mellitus and hypertension, bevacizumab-containing chemotherapy, and panitumumab-containing chemotherapy. The following factors were predictive of serious adverse events in the univariate analysis ($P < 0.05$): age, ECOG score, pre-existing diabetes mellitus and hypertension, bevacizumab-containing chemotherapy, and panitumumab-containing chemotherapy. When these factors were evaluated in the multivariate logistic regression analysis, older age ($P < 0.001$), higher ECOG score ($P < 0.001$), bevacizumab-containing chemotherapy ($P < 0.001$), and panitumumab-containing chemotherapy ($P < 0.001$) were predictive of the development of serious adverse events (Table 3).

The same group of parameters was evaluated in the univariate logistic regression analysis as predictors of fatal adverse events, and among these parameters, only age at diagnosis, ECOG score, pre-existing hypertension, and panitumumab-containing chemotherapy were predictive of fatal adverse events ($P < 0.05$). After including these factors into the multivariate logistic regression analysis, older age ($P < 0.001$), higher ECOG score ($P < 0.001$), and panitumumab-containing chemotherapy ($P = 0.003$) were predictive of fatal adverse events (Table 4).

Table 3 Multivariate logistic regression analysis for factors predicting serious adverse events

Parameters	OR (95% CI)	*P* value
Age (continuous)	1.015 (1.007–1.023)	< 0.001
ECOG		
0	Reference	
1	1.613 (1.363–1.908)	< 0.001
2	2.329 (1.399–3.878)	0.001
Pre-existing hypertension		
Yes	Reference	
No	0.839 (0.671–1.050)	0.125
Pre-existing diabetes mellitus		
Yes	Reference	
No	0.919 (0.662–1.276)	0.614
Concurrent panitumumab treatment		
Yes	Reference	< 0.001
No	0.593 (0.490–0.717)	
Concurrent bevacizumab treatment		
Yes	Reference	< 0.001
No	0.653 (0.519–0.821)	

OR, odds ratio

Table 4 Multivariate logistic regression analysis for factors predicting fatal adverse events

Parameters	OR (95% CI)	*P* value
Age (continuous)	1.046 (1.028–1.064)	< 0.001
ECOG		
0	Reference	
1	1.979 (1.396–2.805)	<0.001
2	3.570 (1.512–8.428)	0.004
Pre-existing hypertension		
Yes	Reference	
No	0.714 (0.475–1.072)	0.104
Concurrent panitumumab treatment		
Yes	Reference	0.003
No	0.589 (0.414–0.838)	

OR, odds ratio

Likewise, the same group of parameters was evaluated in the univariate logistic regression analysis as predictors of hospitalization. The following factors were predictive of hospitalization in the univariate analysis ($P < 0.05$): age, ECOG score, pre-existing hypertension, bevacizumab-containing chemotherapy, and panitumumab-containing chemotherapy ($P < 0.05$). After including these parameters in the multivariate logistic regression analysis, older age ($P < 0.001$), higher ECOG score ($P < 0.001$), bevacizumab-containing chemotherapy ($P < 0.001$), and panitumumab-containing chemotherapy ($P < 0.001$) were predictive of hospitalization (Table 5).

Table 5 Multivariate logistic regression analysis for factors predicting hospitalization

Parameters	OR (95% CI)	*P* value
Age (continuous)	1.015 (1.007–1.023)	< 0.001
ECOG		
0	Reference	
1	1.597 (1.346–1.894)	< 0.001
2	2.089 (1.247–3.484)	0.005
Pre-existing hypertension		
Yes	Reference	
No	0.816 (0.654–1.019)	0.073
Concurrent panitumumab treatment		
Yes	Reference	< 0.001
No	0.612 (0.505–0.742)	
Concurrent bevacizumab treatment		
Yes	Reference	< 0.001
No	0.609 (0.481–0.771)	

OR, odds ratio

Impact of hospitalization on survival outcomes

An additional assessment of the impact of hospitalization on overall and progression-free survival was conducted through the Cox regression analysis. This survival analysis was restricted to patients who did not experience fatal adverse events (2385 patients).

The univariate Cox regression analysis for overall survival included the following factors: age, race, gender, ECOG score, body mass index, primary tumor site, number of organs with distant metastases, bevacizumab-containing chemotherapy and panitumumab-containing chemotherapy, pre-existing diabetes mellitus, and pre-existing hypertension and hospitalization. The following factors were significant in the univariate analysis ($P < 0.05$): ECOG score, body mass index, bevacizumab-containing treatment, and hospitalization. In a multivariate Cox regression model adjusted for (ECOG score, body mass index, and bevacizumab-containing treatment), hospitalization was predictive of worse overall survival (hazard ratio, 1.487; 95% CI, 1.340–1.649; $P < 0.001$).

Similarly, the same group of factors was used in the univariate Cox regression analysis for progression-free survival and the following factors were significant ($P < 0.05$): race, ECOG score, body mass index, bevacizumab-containing chemotherapy, pre-existing diabetes mellitus, and hospitalization. In a multivariate model adjusted for race, ECOG score, body mass index, bevacizumab-containing chemotherapy, and pre-existing diabetes mellitus, hospitalization was predictive of worse progression-free survival (hazard ratio, 1.272; 95% CI, 1.162–1.392; $P < 0.001$).

Discussion

The current study provides an assessment of the predictors of hospitalization among patients receiving different chemotherapy combinations as the first-line treatment of metastatic colorectal cancer. Older age, poorer performance status, and bevacizumab- and panitumumab-containing regimens are associated with a higher risk of hospitalization. Moreover, hospitalization is associated with worse overall and progression-free survival in the multivariate Cox regression model.

There are several weaknesses in the current analysis that need to be clarified; first, hospitalization rates and predictors were not the primary research question of the included studies. Thus, the current study remains technically a retrospective study of prospectively collected datasets. Additionally, some relevant prognostic and predictive information is not available in the current dataset including RAS, BRAF, and MSI statuses. These weaknesses need to be seen through the lens of possible strengths which include the reliance on well-controlled prospectively collected datasets as well as the exclusion of patients with comorbid serious illnesses as part of the eligibility assessment of included studies.

An important caveat for understanding the current study is the highly selective nature of patients included in clinical trials. It is thus expected that—in real-world settings—with older patient population, poorer performance status, higher rates of comorbidity, and less meticulous follow-up, the probability of serious adverse events and hospitalization would be higher.

The fact that more than one-third of all included patients were hospitalized at least once, the point to important cost considerations with regard to the hospitalization of cancer patients [12]. In the context of ongoing discussions about reducing health care costs and optimizing the use of available health care resources, it is important to consider reducing the rates of hospitalization as a possible cost-reducing measure. This might be an important topic for future health care quality projects and research.

The higher rates of hospitalization associated with some patient subsets should be an important discussion point when counseling patients about their systemic therapy options. This is even more relevant given that the aim of treatment in most of those patients is palliative and quality of life is considered as an equally important outcome to survival outcomes in those patients.

The observation of worse overall and progression-free survival among hospitalized patients might be partly related to the fact that some forms of disease progression might manifest as a serious adverse event and subsequently hospitalization (e.g., cancer pain, small bowel obstruction). This indicates the need to meticulously screen hospitalized cancer patients for possible disease progression.

Conclusions

Older age, poorer performance status, and bevacizumab- and panitumumab-containing regimens are associated with a higher risk of hospitalization. Moreover, hospitalization is predictive of worse overall and progression-free survival.

Acknowledgments This publication is based on research using information obtained from www.projectdatasphere.org.

Compliance with ethical standards

Informed consent Informed consent was obtained from all participants included in the study.

Ethical approval All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

References

1. Numico G, Cristofano A, Mozzicafreddo A, Cursio OE, Franco P, Courthod G, Trogu A, Malossi A, Cucchi M, Sirotovà Z, Alvaro MR, Stella A, Grasso F, Spinazzé S, Silvestris N (2015) Hospital admission of cancer patients: avoidable practice or necessary care? PLoS One 10(3):e0120827
2. Brooks GA, Abrams TA, Meyerhardt JA, Enzinger PC, Sommer K, Dalby CK, Uno H, Jacobson JO, Fuchs CS, Schrag D (2014) Identification of potentially avoidable hospitalizations in patients with GI cancer. J Clin Oncol 32(6):496–503
3. Russo CA, Stocks C (2006) Hospitalizations for colorectal cancer, 2006: Statistical Brief #69. 2009 Mar. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US). Available from: https://www.ncbi.nlm.nih.gov/books/NBK54563/. Accessed 10 Jan 2018
4. Oster G (1999) Hospitalization for 5-FU toxicity in metastatic colorectal cancer: incidence and cost. Oncology (Williston Park, NY) 13(7 Suppl 3):41
5. Devani K, Patil N, Simons-Linares CR, Patel N, Jaiswal P, Patel P, Patel S, Savani C, Sajnani K, Young M, Reddy C (2017) Trends in hospitalization and mortality of venous thromboembolism in hospitalized patients with colon cancer and their outcomes: US perspective. Clin Colorectal Cancer 16(3):e199–e204
6. https://www.projectdatasphere.org/projectdatasphere/html/home. Last accessed on 7/10/2017
7. globocan.iarc.fr. Last accessed on 27/11/2016
8. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A et al (2013) Early colon cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 24(Suppl 6):vi64–vi72
9. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Tian Y, Xu F, Sidhu R (2014) Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25(7):1346–1355
10. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, Deeter R, Shahin S, Amado RG (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 27(5):672–680
11. https://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm. Last accessed on 7/10/2018
12. Bansal P, Rabinowitz I, Boumber Y, Bansal D (2017) Cost of colon cancer care: results of nationwide inpatient sample (NIS) data. J Clin Oncol 35(4_suppl):692