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Article

ARTICLE

Clinical Predictors of Early Mortality in Colorectal Cancer Patients Undergoing Chemotherapy: Results From a Global Prospective Cohort Study

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Abstract

Background: Early mortality is a major problem in colorectal cancer (CRC). We have shown that Khorana Score is predictive of early mortality in other cancers. Here, we evaluated the value of this score and other prognostic variables in predicting early mortality in CRC.

Methods:CANTARISK was a prospective, noninterventional, global cohort study in patients with CRC initiating a new chemotherapy regimen. Data were collected at zero, two, four, and six months. Early mortality was defined as death within six months of enrollment. All data were compiled centrally and analyzed after the study closed. Statistically significant univariate associations were tested in multivariable models; adjusted odds ratios (ORs) are presented. Statistical tests were two-sided.

Results: From 2011 to 2012, 1789 CRC patients were enrolled. The median age was 62 years; 71% were Caucasian. One-third (35%) had a rectal primary, and 65% had metastatic disease. There were 184 (10.3%) patients who died during their first six months in the study. For low, intermediate, and high Khorana Score, there were 8.1%, 11.2% and 32.5% deaths, respectively. In multivariable analyses, Khorana Score was an independent predictor of early death (OR for high/intermediate vs low score $= 1.70$, $P = .0027$), in addition to age (OR for each incremental year $= 1.03$, $P = .0014$), presence of metastatic disease (OR $= 3.28$, $P < .0001$), and Easter Cooperative Oncology Group Performance Status Score of 2 or higher (OR $= 3.85$, $P < .0001$).

Conclusions: This study demonstrates that Khorana Score is predictive of early mortality in CRC patients. Intermediate- or high-risk patients, as defined by this score, may benefit from additional interventions aimed at reducing early mortality.

Colorectal cancer is one of the most common malignancies worldwide. In 2013, there were 1.6 million incident cases in the world, with 771 000 deaths (1). While overall survival for various stages of the disease has improved over the last few decades (2), patients receiving chemotherapy for locally advanced or metastatic disease continue to have suboptimal outcomes. In the United States, overall five-year mortality rates are now around 35% for all stages combined (3). For stages III and IV, where the standard of care includes systemic chemotherapy, mortality rates are higher (five-year survival: stage III, 65%–70%, stage IV, 10%–14%) (3,4).

While longer-term trends are clearer, early mortality in these patients has not been well studied, and we do not

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Table 1. Khorana Score*

Variable	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy blood counts	
Hemoglobin < 10 g/dl	1
WBC count $> 11\,000/mm^3$	1
Platelets $\geq 350\,000/mm^3$	1
BMI ≥ 35 kg/m^2	1
Add points for a total score	
Total score	Risk category
0	Low
1–2	Intermediate
≥3	High

*BMI = body mass index; WBC = white blood cell. For all patients in this study, site score of 0 was assigned for colorectal cancer.

understand the factors associated with early death. Most studies have focused on surgery-related morality (5–7). Nowadays, chemotherapy improves survival, is administered for longer durations, and incorporates multiple agents. However, early mortality during the period shortly after the initiation of chemotherapy is not well described. A recent report evaluated six-month mortality in patients receiving adjuvant chemotherapy for resected colon cancer and demonstrated a low overall incidence of such mortality, with advanced age and poor performance status as key predictors (8). A better understanding of predictors of early mortality may help identify patients for more targeted interventions in future studies.

A predictive venous thromboembolism risk score—the Khorana Score—comprising primary site, baseline hemoglobin, leukocyte and platelet counts, and body mass index (Table 1) (9), has been shown to be associated with early mortality in solid tumors (10–12). We have demonstrated previously that the Khorana Score is predictive of six-month mortality after resection of pancreatic adenocarcinoma, even after adjusting for other clinical and pathologic variables (11). However, prospective evaluations of such predictors in other tumor types are lacking. We evaluated the value of the Khorana Score and other key prognostic variables in predicting early mortality for colorectal cancer patients initiating chemotherapy.

Methods

Study Design and Participants

CANTARISK was a prospective, noninterventional, global cohort study sponsored by Sanofi. The objectives were to evaluate venous thromboembolism (VTE), bleeding, and mortality in patients initiating systemic therapy. The study population comprised separate cohorts for colorectal and lung cancer; only the former is analyzed and presented here. The study was open to patients age 18 years or older with a confirmed histopathologic diagnosis of colorectal cancer who were scheduled to begin a new chemotherapy regimen for the index cancer within 15 calendar days of enrollment. Patients were enrolled in 25 countries from May 2011 to July 2012. The planned study sample size was 4300 patients. This sample size was based on the ability to estimate VTE rates and evaluate predictive factors for VTE and mortality with reasonable precision because no formal hypothesis was being tested in this observational study. The estimated VTE rates were 5% and 4% in lung and colorectal cancer patients, respectively. For lung cancer, 1500 patients will allow detection of an odds ratio of 2.7 to have a proven VTE, with 80% power, when the predictive factor is present in 15% to 80% of patients. An additional 650 patients for validation of the predictive factor would require a total of 2150 patients. Similarly, for colorectal cancer, 1500 patients will allow detection of an odds ratio of 3.1 to have a proven VTE, with 80% power, when the predictive factor is present in 15% to 80% of patients. An additional 650 patients for validation of the predictive factor would require a total of 2150 patients. However, funding for the study was terminated by the sponsor midway during enrollment; by then 3769 (87.7% of planned) patients had been enrolled. Data for all colorectal cancer patients are presented in this report. This study was observational, under real practice conditions, with only the available clinical data being collected; there were no additional visits or procedures associated with participation. The decision regarding the chemotherapy treatment administered to patients included in this study was taken prior to enrollment and was not linked to patient participation. Patients participating in other studies that necessitated blinding of treatment were excluded from participating in this study. Each patient was to be followed for six months following enrollment. All patients provided written informed consent at enrollment.

Data Collection

Steering committee members in each participating country were invited and selected after an initial phase of study documentation provision and review of study policies and procedures. Steering committee members then selected appropriate physicians in their respective countries, who were trained for participation in the study. These physicians enrolled patients meeting eligibility criteria in consecutive fashion to minimize selection bias. For quality control, a screening log was also maintained for documentation of reasons for nonenrollment of patients. For each enrolled patient, all data were collected using an electronic case report form (eCRF) that was created a priori by the study team. Baseline data collected at the inclusion visit comprised demographics, medical history, cancer diagnosis details, cancer treatment history (including surgery, chemotherapy and biologic therapies, radiation therapy), bleeding and thrombosis history, concomitant medication use history, and laboratory testing results (complete blood count, serum chemistry, coagulation profile). Data were collected at two-, four-, and six-month visits after the inclusion visit. These included subsequent cancer treatment details, bleeding and thromboembolic episodes, laboratory testing results, concomitant medications, and cancer progression and survival data. Specific investigations to detect occult or asymptomatic venous thrombosis were not performed prospectively at these visits. Such investigations were performed as indicated based on clinical symptoms or physical signs suggestive of VTE. All data were those values available at a date as close as possible to the corresponding study visit. Automatic requests were generated by the eCRF, in case of inconsistencies, to the physician, who was obliged to respond by confirming or modifying the data questioned. Data quality control was planned to be performed on site in 10% of active sites chosen at random in each country or if specific issues were recognized at some sites. This quality control was performed by qualified designated personnel in each country.

Statistical Analyses

Early mortality was defined as death within six months of enrollment in the study. Venous thromboembolism was identified by clinical suspicion of a new event during follow-up. Specific testing for such events was up to the discretion of the treating physician. The quantitative variables were summarized using the number of nonmissing data, mean, standard deviation, median, and extreme values. The qualitative variables were summarized using the number of nonmissing data, counts, and percentages. No imputation for missing values was performed. To evaluate the predictive role of independent variables, binary logistic regression was used, with early mortality as the outcome. Univariate analyses were performed for various predictors; statistically significant univariate associations and a priori prognostic variables were tested in multivariable models. Covariate interactions were tested, and highly correlated variables (such as history of anemia and baseline hemoglobin, intact primary tumor and metastatic disease) were tested separately; the variable with higher statistical significance was included. The final multivariable model was parsimonious, derived by stepwise removal of predictors with least statistical significance (highest *P* values) to minimize problems from multiple comparisons. Odds ratios (ORs) are presented with 95% confidence intervals (CIs) and *P* values. All statistical tests were two-sided; *P* values of less than .05 were considered statistically significant. All analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Results

Study Population

The study population consisted of 1789 patients with colorectal cancer who were enrolled into the registry. Baseline demographic and clinical characteristics are described in Table 2. Of note, the median age was 62 years; 71% of patients were Caucasian; approximately one-third of patients had a rectal primary, and 20% had received prior chemotherapy for the index cancer. Data on mutational profile were available for only a minority of patients. Mutations in *EGFR* were seen in 59% (n = 44/75), *KRAS* in 43% (n = 193/447), and *BRAF* in 6% (n = 3/50).

Univariate Analyses

A total of 184 (10.3%) patients died within their first six months in the study. We evaluated the association of baseline variables with early mortality. Increasing age, lower body mass index (BMI), lower hemoglobin, higher white blood cell (WBC) count, higher platelet count, an intact primary tumor, presence of metastatic disease, an Eastern Cooperative Oncology Group (ECOG) Performance Score (PS) of 2 or higher, and baseline anemia were associated with early death (Table 3). Khorana Score, which incorporates many of these variables, as described in Table 1, was associated with early death. For patients in the low-, intermediate-, and high-risk Khorana Score categories, there were 8.1% (n = 80/985), 11.2% (n = 64/571), and 32.5% (n = 13/40) who died within six months, respectively (chi-square $P_{trend} < .0001$). Of note, there was no statistically significant association between early mortality and VTE, sex, race, geographic region, location of primary tumor (colon or rectum), or various comorbidities (history of anemia, hypertension, diabetes, arterial disease, pulmonary embolism or deep venous thrombosis, heart failure, chronic obstructive pulmonary disease, or major non-cancer-related surgery within the prior six months).

Table 2. Baseline demographic and clinical characteristics*

Age, median (range), y	62 (19–91)
Males, No. (%)	1094 (61)
Race (missing = 49), No. (%)	
White	1237 (71)
Asian	308 (18)
Black	65 (4)
Others	130 (7)
Region, No. (%)	
North America	502 (28)
South America	212 (12)
Europe	666 (37)
Asia and rest	409 (23)
ECOG PS (missing = 69), No. (%)	
0	885 (51)
1	710 (41)
≥2	125 (8)
Smoker (missing = 31), No. (%)	
Never	1008 (57)
Former	502 (29)
Active	248 (14)
Hypertension (missing = 21), No. (%)	645 (36)
Diabetes (missing = 3), No. (%)	310 (17)
Arterial disease† (missing = 68), No. (%)	151 (9)
PE or DVT (missing = 3), No. (%)	43 (2)
Major surgery in prior 6 mo‡ (missing = 3), No. (%)	72 (4)
Years since diagnosis (missing = 9), median (range)	0.2 (0–27)
Primary tumor location, No. (%)	
Colon	1162 (65)
Rectum	627 (35)
Metastatic disease (missing = 3), No. (%)	1162 (65)
Prior chemotherapy, No. (%)	363 (20)
BMI, median (range), kg/m^2 (missing = 6)	25 (13–58)
Hemoglobin, median (range), g/dl (missing = 118)	12.4 (7.2–18.4)
WBCs, median (range), ×1000/mm^3 (missing = 163)	7.2 (1.7–24)
Platelets, median (range), ×1000/mm^3 (missing = 164)	271 (26–871)
Khorana Score (missing = 193), No. (%)	
Low (0)	985 (62)
Intermediate (1–2)	571 (36)
High (≥3)	40 (2)

*For continuous variables, the median is presented, with range within parentheses. For categorical variables, the number is presented, with percentage within parentheses. BMI = body mass index; DVT = deep venous thrombosis; ECOG PS = Eastern Cooperative Oncology Group Performance Score; PE = pulmonary embolism; VTE = venous thromboembolism; WBC = white blood cell.
†Arterial disease is a composite of a history of myocardial infarction, cerebrovascular stroke, coronary artery disease, or peripheral artery disease.
‡Other than cancer surgery.

A total of 92 (5.1%) patients experienced a new VTE. A higher BMI, presence of a central venous catheter, worse ECOG PS, and intermediate/high Khorana Score were associated with VTE. Of note, there was no statistically significant association between new VTE and age, comorbidities, major non-cancer-related surgery within the prior six months, leg immobilization within the prior 30 days, distant metastatic disease, presence of intact primary tumor, active smoking, or prior history of venous thromboembolic disease.

Multivariable Analyses

Multivariable analyses showed that hemoglobin, WBC count, platelet count, BMI, age, metastatic disease, and ECOG PS were the final variables statistically significantly associated with early mortality. Replacement of the first four variables with the

Table 3. Univariate analyses of predictors of early (within 6 months) death*

	OR (95% CI)	P
Age, each incremental year	1.02 (1.01 to 1.03)	.003
Hemoglobin, each incremental g/dl	0.75 (0.69 to 0.82)	<.0001
WBC count, each incremental $\times 1000/mm^3$	1.21 (1.15 to 1.26)	<.0001
Platelet count, each incremental $\times x1000/mm^3$)	1.00 (1.00 to 1.03)	.01
BMI, each incremental kg/m^2	0.95 (0.92 to 0.98)	.0004
BMI, ≥ 25 kg/m^2 vs < 25 kg/m^2	0.60 (0.44 to 0.81)	.001
Anemia, yes vs no	2.27 (1.63 to 3.16)	<.0001
Intact primary tumor, yes vs no	2.31 (1.64 to 3.25)	<.0001
Metastatic disease, yes vs no	3.99 (2.57 to 6.20)	<.0001
ECOG PS, ≥ 2 vs 0/1	2.23 (1.79 to 2.79)	<.0001
Khorana Score, intermediate vs low	1.43 (1.01 to 2.02)	.04
Khorana Score, high vs low	5.45 (2.71 to 10.97)	<.0001

*BMI = body mass index; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Score; OR = odds ratio; WBC = white blood cell.

Table 4. Multivariable analysis of predictors of early (within 6 months) death for all patients (n = 1533)*

	OR (95% CI)	P
Age, each incremental year	1.03 (1.01 to 1.04)	.0014
Khorana Score, intermediate/high vs low	1.70 (1.20 to 2.41)	.0027
Metastatic disease, yes vs no	3.28 (2.03 to 5.30)	<.0001
ECOG PS, ≥ 2 vs 0/1	3.85 (2.37 to 6.25)	<.0001

*Odds ratios are two-sided. P values are two-sided. CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Score; OR = odds ratio.

Table 5. Multivariable analysis of predictors of early (within 6 months) death for patients with metastatic disease (n = 1014)*

	OR (95% CI)	P
Age, each incremental year	1.02 (1.00 to 1.04)	.024
Khorana Score, intermediate/high vs low	1.69 (1.16 to 2.46)	.006
ECOG PS, ≥ 2 vs 0/1	3.68 (2.17 to 6.24)	<.0001

*Odds ratio are adjusted. P values are two-sided. CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group Performance Score; OR = odds ratio.

Khorana Score led to a more robust final model (Table 4). This model showed that Khorana Score was an independent predictor of early death (OR for high/intermediate vs. low score = 1.70, $P = .0027$), in addition to age (OR for each incremental year = 1.03, $P = .0014$), presence of metastatic disease (OR = 3.28, $P < .0001$), and ECOG performance status ≥ 2 (OR = 3.85, $P < .0001$). In a separate multivariable model for only patients with metastatic disease, the same variables were of statistical significance (Table 5).

Presence of a central venous catheter (OR = 4.01, 95% CI = 2.32 to 6.94, $P < .0001$), ECOG PS of 2 or higher (OR = 2.17, 95% CI = 1.07 to 4.43, $P = .03$), and intermediate/high Khorana Score (OR = 1.82, 95% CI = 1.15 to 2.87, $P = .01$) were associated with VTE.

Discussion

We demonstrate that a simple risk score comprising data collected routinely on all patients undergoing cancer care can predict early mortality in patients receiving chemotherapy for colorectal cancer. In addition to the usual clinical practice of assessing ECOG PS, the Khorana Score provides further value in identifying high-risk patients. Our study is one of the few prospective global cohort studies to focus specifically on predictive factors for early mortality in this population. No investigations or interventions in addition to standard clinical care were introduced; therefore, a real-world scenario is evaluated, making the results widely applicable. By identifying high-risk patients early, it may be possible to target specific interventions in this group, with the ultimate goal of reducing such mortality.

There are several studies assessing the risk of death following surgical resection of colorectal cancer (5–7). However, studies of chemotherapy focus primarily on overall survival and not on early mortality. A consistent definition of early mortality in this patient population is lacking; we focused on the six-month time point because most chemotherapy regimens for colorectal cancer are administered for at least six months and this definition is most accepted (8). Mortality during this time period may be from multiple causes—patient-, disease-, and therapy-related factors.

Our final model includes the well-established risk factors—age, performance status, and stage of disease (13–15). The Khorana Score is an independent predictor, and its components add novel predictive value. Site of cancer is moot in this analysis because all cases are of colorectal cancer. Low hemoglobin has been associated with poorer clinical outcomes in studies of colorectal (16) and other cancers (17–19). We demonstrate incremental improvement in the odds of six-month survival with improving baseline hemoglobin. Leukocytosis, a well-known marker of inflammation, has been associated with worse outcomes in many cancers (20). In colorectal cancer, a meta-analysis of four large randomized clinical trials of firstline chemotherapy for metastatic colorectal cancer showed that 60-day mortality was higher, with a baseline leukocyte count higher than $8000/mm^3$ (21). A previous meta-analysis of clinical trials of 5-fluouracil in metastatic colorectal cancer showed similar results—survival was poorer in patients with a baseline leukocyte count higher than $10\,000/mm^3$ (22). In parallel, thrombocytosis also reflects physiologic inflammatory response and has been shown to be associated with worse survival in colorectal cancer (16,22) and breast cancer (23). The cutoffs used in the latter studies are similar to the Khorana Score—platelet counts higher than $350–400 \times 1000/mm^3$.

The final model is robust—across adjuvant and metastatic settings, and for all locations of the primary tumor. There are data to indicate differential outcomes for different primary subsites within the colorectum (24,25); however, that was not observed in our data set. More precise information on the exact location of the primary tumor (right-sided vs left-sided, for example) was not available, however. A recent large pooled analysis of 37 568 patients enrolled in 25 clinical trials of adjuvant chemotherapy for resected colon cancer showed that six-month overall mortality was low (1.4%) (8). This is somewhat expected, given that the study population was otherwise healthy individuals with resected colon cancer; our analysis included all patients receiving otherwise off-study therapy for resected and metastatic disease. A predictive nomogram from the pooled analysis included age, performance score, tumor grade, T-stage, positive lymph node ratio, and decade when treated. Age, performance score, and disease stage were captured in our model as well, making these findings more reliable. The hematologic components of the Khorana Score were not evaluated in the pooled analysis, however.

Body mass index has been studied extensively in colorectal and other cancers, and results are discrepant. The aforementioned pooled analysis did not show an association between BMI and mortality (8). Another pooled analysis of more than 21 000 patients across 25 clinical trials of firstline chemotherapy in metastatic colorectal cancer showed increased mortality with lower baseline BMI (26). Visceral adiposity, meanwhile, has been shown to be associated with higher mortality in patients receiving adjuvant chemotherapy for colorectal cancer (27). These results likely reflect competing causes. A low baseline BMI is probably reflective of cancer-related weight loss. A high BMI—in the obese category—is likely associated with comorbidities. This was demonstrated in a large meta-analysis of approximately 60,000 patients across 16 cohort studies of long-term follow-up: a low BMI was associated with higher colorectal cancer–related mortality, and a high BMI was associated with higher all-cause mortality (28). Another large study showed similar results—a heterogeneity in the association of BMI with colorectal cancer–related mortality, depending on timing of BMI values (29).

The association of Khorana Score with VTE has previously been shown and validated in multiple prospective and retrospective studies generally in heterogeneous solid tumor populations (9,10,30,31), and the current analysis further extends these data in a single site of cancer. We also note that while both VTE and early mortality were associated with the Khorana Score, early deaths were not associated with venous thromboembolic events. This has been observed previously—in a prospective study, Khorana Score predicted VTE risk and death, but not death after cancer-associated VTE. It is likely that early VTE events are not associated with mortality, whereas later events are (10). Therefore, the Khorana Score appears to capture physiologic and pathologic factors beyond those related simply to VTE.

Finally, using the Khorana Score—as opposed to individual components—in the final model allows for a more parsimonious model with increased predictive value, and cutoffs of component variables allow more precise delineation of patients into different risk categories. Our results allow identification of high-risk patients, and they represent a first step in this process. Future studies should incorporate this score to allow further validation and consider methods to mitigate the risk in patients identified by this score. At this time, it is not clear how we can influence components of the Khorana Score meaningfully in the clinical setting.

Our study has limitations. Total planned accrual goal was not met as funding was withdrawn prior to completion. Nonetheless, this is a large global cohort study, allowing assessment of clinical predictors, and the study population is somewhat heterogeneous, consisting of patients at various stages of disease and in different lines of therapy. However, metastatic disease is shown to be associated with mortality, adding to the validity of results. Detailed information on chemotherapy adverse effects and dose modifications was not collected because this was not an interventional study. Bevacizumab, used often for treatment of metastatic colorectal cancer, is associated with bleeding and thrombosis risks. However, specific details on its use were not available; therefore, we were unable to control for it in our analyses. Also, mutational testing was not dictated centrally; exact details of extent of *RAS* and *RAF* testing and types of tests used by individual doctors and laboratories worldwide are not available. Due to these limitations, these findings cannot be considered definitive or practice-changing. However, the robust estimates in a large global cohort lend credibility to the findings, supporting evaluation in prospective clinical trials.

In summary, we demonstrate in a prospective global study that early mortality remains a considerable problem in colorectal cancer. A simple set of clinical variables can identify patients at high risk, allowing future studies to target specific interventions in this subgroup of patients with the goal of reducing such mortality. Incorporation of this score in prospective clinical trials can allow further validation.

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