Original Article

Bone marrow tolerance during postoperative chemotherapy in colorectal carcinomas

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Background: This study seeks to quantify and compare bone marrow tolerance during postoperative chemotherapy therapy between rectal cancer *vs.* colon cancer patients. During rectal cancer treatment, patients receive neoadjuvant chemoradiation (CRT) irradiation which can exacerbate the hematologic toxicity (HT) via incidental irradiation of the pelvic bone marrow (PBM) during myelosuppressive postoperative chemotherapy. In contrast, colon cancer patients receive the same postoperative myelosuppressive chemotherapy but do not routinely receive preoperative chemoradiation therapy. This comparison will help elucidate the lasting myelosuppressive effects of incidental pelvic bone marrow (PBM) irradiation on rectal cancer patients during neoadjuvant preoperative chemoradiation therapy.

Methods: Rectal cancer patients treated with preoperative CRT followed by postoperative 5-Fluorouracil and oxaliplatin (OxF) chemotherapy (n=35) were compared to colon cancer patients who received only postoperative OxF chemotherapy (n=42). End points were ≥ grade 3 hematologic toxicity (HT3) or hematologic event (HE) defined as ≥ grade 2 HT and a dose reduction in OxF. Wilcoxon rank sum test tested continuous variables and Chi-squared test measured differences in categorical variables. HT3 and HE probability during postoperative chemotherapy was estimated with Kaplan-Meier curves and Cox regression analysis.

Results: During OxF chemotherapy, 40.0% (n=14) of rectal cancer patients experienced HT3 compared to 26.1% (n=11) of colon cancer patients (P=0.4). HE was experienced by 48% (n=17) of rectal cancer patients compared to 36% (n=15) of colon cancer patients (P=0.36). Rectal cancer patients were likelier to experience HT3 on multivariable cox regression analysis, controlling for several clinical covariates, with a hazard ratio (HR) of 2.49, [(95% CI: 1.02–6.02), P=0.045] than colon cancer patients. While rectal cancer patients were more likely to experience HE than colon cancer patients on multivariable Cox regression analysis with a HR of 1.8 (95% CI: 0.95–3.75), this only trended in statistical significance, P=0.07.

Conclusions: Rectal cancer patients are more likely than colon cancer patients to experience hematologic toxicities impacting the tolerance of standard of care chemotherapeutics during adjuvant therapy. Focused PBM sparing during radiation therapy for rectal cancer patients may improve tolerance of myelosuppressive chemotherapeutic agents delivered in the postoperative setting.

Keywords: Hematologic toxicity (HT); bone marrow; chemoradiation; rectal cancer; colon cancer

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Introduction

Colorectal cancer in the United States is expected to account for approximately 93,000 new cases of colon cancer and 40,000 of rectal cancer in 2016 (1). For stage III colon cancer, surgical resection followed by adjuvant chemotherapy consisting of 5-Flurouracil (5-FU) and oxaliplatin based chemotherapy (OxF) is the preferred treatment strategy (2,3). This is in contrast to the management of locally advanced rectal cancer (T3/T4 or lymph node positive) which consists of preoperative chemoradiation therapy (CRT) (4) followed by total mesorectal excision, and often postoperative chemotherapy consisting of OxF (5).

There have been several studies evaluating the relationship between incidental pelvic bone marrow (PBM) irradiation and hematologic toxicity (HT) during CRT (6,7) in an attempt to create radiotherapy dose constraints to the PBM. Since nearly 40% of total human bone marrow (BM) (8) is in the PBM, sparing of the BM is thought to limit morbidity during the short period of CRT. However, in reality, irradiating bone marrow (BM) is likely to result in long term myelosuppression since there can be injury to BM stem cells (9) as well as declines in stromal volume which provide stimulating factors crucial for normal hematopoiesis (9).

Since oxaliplatin itself is myelosuppressive, rectal cancer patients receiving adjuvant/consolidative OxF chemotherapy may experience difficulty tolerating this regimen given the prior PBM stress endured during CRT. This may explain why rates of ≥grade 3 HT (HT3) for rectal cancer patients during CRT are 10% (10) and nearly 40% during postoperative OxF therapy (5). Interestingly colon cancer patients, who do not receive prior CRT, experience similar rates of HT3 of nearly 35%, and those above the age of 70 experience rates as high as 40 % during adjuvant therapy (11).

However, what is not well reported in the literature is the timing of when rectal cancer patients experience HT3 compared to colon cancer patients or whether they require more dose reductions during adjuvant chemotherapy.

This study sought to compare the rates and timing of HT3 during postoperative chemotherapy in rectal cancer patients, who receive preoperative chemoradiation *vs.* colon cancer patients who do not. We hypothesized that rectal cancer patients would experience more instances of HT3 at earlier time points compared to colon cancer patients who do not receive preoperative CRT. The secondary endpoint of this study was to evaluate the rate and timing of a hematologic event (HE) defined as a ≥grade 2 HT along with a dose reduction or missed dose of chemotherapy.

Methods

Patient inclusion criteria

After Institutional Review Board (IRB) approval, we conducted a retrospective study of rectal cancer patients who were treated with preoperative CRT at this institution (12) and colon cancer patients treated with postoperative chemotherapy. Patients' chemotherapy during CRT must have consisted of capecitabine or infusional 5-FU. Patients who received concurrent oxaliplatin during CRT were excluded. Postoperative chemotherapy must have consisted of OxF (modified FOLFOX-6 or CapeOx) resulting in 35 patients. No prospective trials have demonstrated differences in HT of CapeOx compared to modified FOLFOX-6 (13). Three rectal cancer patients and one colon cancer patient with oligometastatic disease were included, as these patients were treated with curative intent and with a similar number of chemotherapy cycles. Furthermore, additional treatment with bevacizumab does not alter the HT profile in addition to FOLFOX (14). Colon cancer patients must have been treated with OxF adjuvant chemotherapy after surgery (Stage III), with available weekly complete blood cell (CBC) counts leading to 42 patients.

Radiation treatment planning

Rectal cancer patients underwent radiation treatment consistent with Radiation Therapy Oncology Group treatment guidelines for rectal cancers (12,15,16). Patients were treated with either intensity-modulated radiation therapy (IMRT) (n=20, 57.1%) or 3D-conformal radiation therapy (3D-CRT) (n=15, 42.8%) to a median dose of 50.4 Gy (range: 48.6–54 Gy) in 1.8 Gy/day fractions. Patients receiving Intensity Modulated Radiation Therapy (IMRT) were treated as per RTOG 0822 with additional institutional dose constraints consisting of the iliac bone marrow (IBM) and femoral head volume receiving 30 Gy <50% (17,18). Similarly, the median volume receiving 30 Gy to the IBM for rectal cancer patients in this study was 37%.

Chemotherapy delivery

Rectal cancer patients during neoadjuvant CRT were treated with capecitabine (825 mg/m^2 orally twice daily) or with

5-FU (225 mg/m^2/day). All patients received postoperative adjuvant OxF, primarily with modified FOLFOX-6 protocol consisting of Folinic acid (400 mg/m^2) and oxaliplatin (85 mg/m^2) on day 1, 5-Fluoruracil (400 mg/m^2) on day 1 followed by 2,400 mg/m^2 over 46 hours in two week cycles for up to 12 cycles. For Rectal cancer patients, the adjuvant chemotherapy duration was determined by subtracting days on CRT from total planned days of adjuvant treatment. Colon cancer patients were also treated in a similar manner with modified FOLFOX-6. Four rectal cancer patients and one colon cancer patient received CapeOx as adjuvant treatment given as capecitabine (850 mg/m^2 orally twice daily) and Oxaliplatin (130 mg/m^2 on day one) for up to 8 cycles every 3 weeks. No prospective trials have demonstrated differences in HT of CapeOx compared to modified FOLFOX-6 (13).

Hematologic toxicity

Both colon cancer and rectal cancer patients had weekly CBCs during postoperative chemotherapy. HT3 was graded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0. HE was defined as HT3 or ≥grade 2 HT plus a dose reduction or missed dose of adjuvant OxF therapy as a direct result of the HT.

Statistical analysis

The Shapiro-Wilk test was first done to test for normal data distribution. Categorical variables were described as the absolute number and percentage, and continuous variables were described by the median and interquartile ranges (IQR) due to right-skewed distribution. Chi-square tests and Fisher's exact test (if expected frequencies were <5) were used to analyze categorical data.

Kaplan-Meier curves and log rank test were used to estimate and compare HT3-free and HE-free progression during adjuvant therapy in rectal cancer *vs.* colon cancer. Patients were censored at the last day of completion of adjuvant chemotherapy. Cox regression analysis was done to assess the hazard ratio of experiencing HT3. All p values were 2-sided with a level <0.05 considered as significant. All statistics and graphs were calculated and created using R software 3.2.0 (Vienna, Austria, http://www.R-project.org).

Results

Patient characteristics

Patients' baseline characteristics are detailed in *Table 1*. There were 35 rectal cancer patients evaluated with a median age of 53 years, the majority being males (80%). Most patients had node positivity found during clinical staging (72%). During CRT, patients were mostly treated with IMRT (57.1%) and capecitabine (82.9%). During postoperative OxF chemotherapy, rectal cancer patients received FOLFOX (83%), FOLFOX/Bevacizumab (8.6%) and CapeOx (8.6%). There were 42 colon cancer patients evaluated with a median age of 60.5 years, and 52.4% were males. All colon cancer patients had node positive disease on pathological staging and the majority were treated with FOLFOX only (95.2%) with one patient receiving CapeOx (2.4%) and one receiving FOLFOX with bevacizumab (2.4%).

Hematologic toxicity during postoperative chemotherapy

Table 2 reveals that during adjuvant chemotherapy for rectal cancer, 40% (n=14) of patients experienced HT3 compared to 26.1% (n=11) in the colon cancer group (P=0.4). HE occurred in 48% (n=17) of rectal cancer patients versus 36% (n=15) in colon cancer group, (P=0.36). Rectal cancer patients mainly experienced HT3 consisting of leukopenia 25.7% (n=9), neutropenia 20.0% (n=7), and thrombocytopenia 2.9% (n=1) while none were due to anemia. There were 11.4% (n=4) who experienced both HT3 leukopenia and neutropenia. In the colon cancer group, there were 9.5% (n=4) patients who had HT3 leukopenia, 9.5% (n=4) had neutropenia, and 7.1% (n=3) had anemia, with 4.8% (n=2) having both leukopenia and neutropenia. There were 25.8% (n=9) of rectal cancer patients that required pegfilgrastim support during adjuvant chemotherapy compared to 11.9% (n=5) in colon cancer group (P=0.20).

Clinical parameters

Table 3 describes the association between clinical parameters (age, BMI, gender, total time from surgery until adjuvant therapy) and HT3/HE for rectal cancer patients and colon cancer patients. Interestingly, no clinical parameters, including total time from surgery until adjuvant therapy

Table 1 Patient baseline characteristics

Patient characteristics	Rectal cancer	Colon cancer
Patient number (n)	35	42
Age median (IQR)	53 (13.5)	60.5 (15.0)
BMI median (IQR)	29.2 (7.8)	27.9 (8.4)
Sex, n (%)		
Male	28 (80.0)	22 (52.4)
Female	7 (20.0)	20 (47.6)
Mode, n (%)		
3DCRT	15 (42.8)	NA
IMRT	20 (57.1)	
cTNM, n (%)		
T1	1 (2.9)	1 (2.4)
T2	2 (5.7)	7 (16.7)
T3	31 (88.6)	34 (81.0)
T4	1 (2.9)	0 (0)
N0	8 (22.9)	0 (0)
N1	21 (60.0)	30 (71.4)
N2	6 (17.1)	12 (28.6)
M0	32 (91.4)	41 (97.6)
M1	3 (8.6)	1 (2.4)
Total adjuvant		
Chemotherapy days [median (IQR)]	138 (48.5)	163 (17.2)
Total elapsed days of neoadjuvant CRT median (IQR)	38 (5.0)	NA
Neoadjuvant chemotherapy		
Capecitabine	29 (82.9)	NA
5-Flurouracil	6 (17.1)	
Adjuvant OxF therapy n (%)		
FOLFOX	29 (83.0)	41 (95.2)
Capecitabine/Ox	3 (8.6)	1 (2.4)
FOLFOX/Bevacizumab	3 (8.6)	1 (2.4)

IQR, interquartile range; BMI, body mass index; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiation therapy; FOLFOX, folinic acid, 5-Fluorouracil, oxaliplatin; cTNM, clinical staging.

Table 2 Hematologic toxicity experienced during postoperative chemotherapy

Treatment	Rectal n=35 [number (%)]	Colon n=42 [number (%)]	P values
HT3 rate	14 (40.0)	11 (26.1)	0.4
HE rate	17 (48.0)	15 (36.0)	0.36
WBC			0.11*
Nadir median (range)	2.7 (1.5–7.7)	3.4 (1.2–8.1)	
Grade 0	8 (22.9)	18 (42.9)	
Grade1	7 (20.0)	6 (14.29)	
Grade2	11 (31.4)	15 (11.9)	
Grade3	9 (25.7)	4 (9.5)	
ANC			0.33*
Nadir median (range)	1.7 (0.5–6.2)	1.8 (0.29–6.10)	
Grade 0	14 (0.4)	18 (42.9)	
Grade 1	6 (17.14)	6 (14.29)	
Grade 2	10 (28.5)	15 (35.7)	
Grade 3	7 (20.0)	4 (9.5)	
Median			NA
Platelet nadir (range)	132 (78.0–245.0)	139 (78.0–238.0)	
Grade 0	26 (74.3)	8 (19.0)	
Grade 1	8 (22.9)	6 (14.2)	
Grade 2	1 (2.85)	1 (2.38)	
Grade 3	0 [0]	0 [0]	
Median hemoglobin nadir (range)	11.9 (7.9–14.0)	11.4 (5.2–14.5)	0.74*
Grade 0	16 (45.71)	12 (28.57)	
Grade 1	9 (25.71)	22 (52.38)	
Grade 2	9 (25.71)	6 (14.2)	
Grade 3	1 (2.85)	3 (4.76)	
Growth factor support adjuvant pegfilgrastim	9 (25.7)	5 (11.9)	0.2
Dose reduction adjuvant	18 (51.4)	13 (30.9)	0.11
Surgery to start adjuvant therapy median (IQR)	49 (30.0)	41.5 (45.0)	0.07†

*, P value Chi-square or fisher exact comparing HT3 rates between colon cancer and rectal cancer; †, Wilcoxon-Rank Sum test. WBC, white blood cells; ANC, absolute neutrophil count; NA, no applicable analysis as there were 0 grade 3 events.

seemed to have associated with HT3 or with HE.

Time to ≥ grade 3 hematologic toxicity

Figure 1 demonstrates Kaplan-Meier curves that show probability of being free of HT3 over the course of treatment. Log-rank analysis revealed a p value of 0.065. Univariate Cox regression revealed the hazard ratio (HR) to be 1.8 (0.95–3.75, P=0.07). Multivariate Cox regression analysis, when adjusting for total days from surgery until starting chemotherapy, gender, and age demonstrated that rectal cancer patients were at an increased risk of HT3

Table 3 Clinical parameters correlated with a hematologic event or >Grade 3 hematologic toxicity

Clinical parameter	Rectal cancer OR (95% CI); P value	Colon cancer OR (95% CI); P value
Age		
HT3	4.77 (0.14–20.0); 0.3	0.47 (0.11–1.94); 0.3
HE	1.005 (0.98–1.02); 0.54	0.99 (0.98–1.01); 0.6
BMI		
HT3	0.93 (0.82–1.19); 0.86	0.68 (0.17–2.7); 0.59
HE	0.98 (0.95–1.01); 0.29	0.99 (0.97–1.01); 0.34
Male gender		
HT3	0.86 (0.16–4.6); 0.29	0.41 (0.09–1.17); 0.22
HE	1.07 (0.70-1.3); 0.73	0.79 (0.59–1.06); 0.134
Days between surgery and adjuvant therapy	0.99 (0.98–1.001); 0.63	0.99 (0.97–1.06); 0.56
	0.99 (0.98–1.01); 0.64	1.00 (0.99–1.01); 0.61
3DCRT *vs.* IMRT	1.33 (0.28–1.66); 0.09	NA*
Capecitabine *vs.* 5FU	0.93 (0.16–5.4); 0.94	NA*
Total radiation dose	1.006 (0.99–1.01); 0.15	NA*

*, NA is not an applicable parameter to colorectal patients. OR, odds ratio; CI, confidence interval; BMI, body mass index; 3DCRT, 3-dimensional conformal therapy; IMRT, intensity modulated radiation therapy; NA, not applicable.

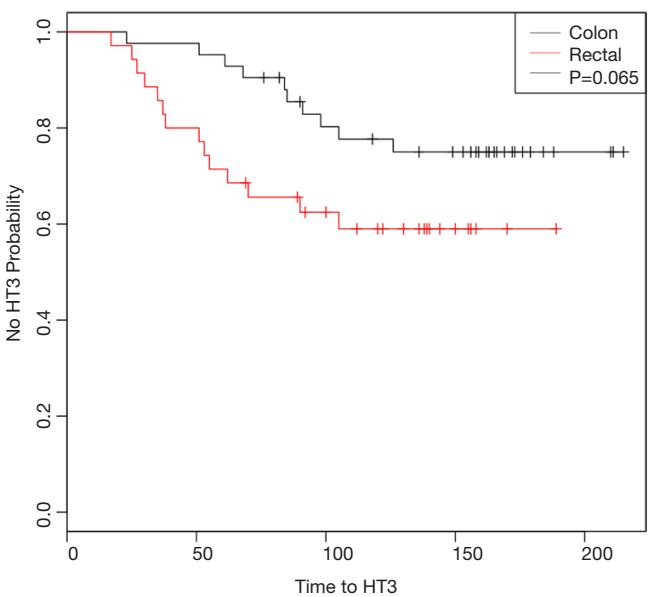

Figure 1 Kaplan Meier curve comparing time to HT3.

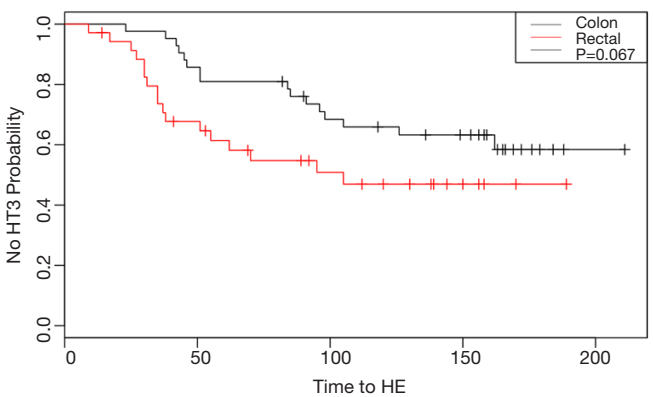

Figure 2 Kaplan-Meier curve comparing time to HE. HE, hematologic events.

(HR =2.49; 95% CI: 1.02–6.02, P=0.045).

Time to hematologic event

Figure 2 demonstrates a Kaplan-Meier curve showing the probability of being HE-free during the course of OxF treatment. Log-rank analysis demonstrates a P value of 0.067. Univariate Cox regression analysis demonstrated the HR to be 1.8 (95% CI: 0.94–3.5, P=0.07). Multivariate Cox regression analysis adjusting for total days from surgery until starting chemotherapy, gender, and age demonstrated a HR of 2.07 (95% CI: 0.99–4.3, P=0.053).

Discussion

In this patient sample, we were able to demonstrate that rectal cancer patients experience HT3 sooner on multivariate analysis while adjusting for imperative covariates. We believe that the earlier timing of hematologic complications in rectal cancer is a reflection of underlying incidental injury to the pelvic bone marrow from prior radiation therapy. This has clinical implications for not only more cautious sparing of the PBM during CRT but also suggests increased hematologic morbidity amongst rectal cancer patients. Although pegfilgrastim use was not statistically significantly greater when used in rectal cancer patients compared to colon cancer, its use was nearly doubled in the rectal cancer group compared to colon cancer. These findings underscore the importance of PBM sparing during CRT as durable injury to the BM may make the added stress of cytotoxic chemotherapy less tolerable. We suspect though given a larger sample size this would become more evident, given the literature suggesting decreased marrow reserve after irradiation.

Radiation to the PBM had been implicated in diminishing long term BM function. During CRT there is injury to quiescent BM stem cells and stromal supporting elements (19) when examining in vitro cells ($CD34^+$) and human bone marrow (20,21). A recent study examined patients treated with capecitabine and radiation for rectal cancer (similar to our cohort) and found that there are decreases to the mean proton density fat fraction (PDFF), crucial for supporting hematopoiesis, when comparing MRIs before and after CRT (22). For these two reasons, the BM may have less marrow reserve to tolerate ensuing insults (19,23,24). There are no uniform tables to guide clinicians about pelvic bone marrow sparing, as the bone marrow was not allotted dose constraints in the original normal tissue toxicity from radiation tables by Emami (25).

While we found higher rates of HT3 and HE in rectal cancer patients compared to colon cancer patients, we were unable to demonstrate so with statistical significance. We believe though that our sample was underpowered (mainly due to strict inclusion criteria to ensure homogeneity) to demonstrate the differences in rates of HT3 and HE although we suspect rectal cancer patients experience these events in greater numbers compared to colon cancer.

This study had several strengths, namely homogeneity amongst patient samples. In order to ensure that the long-term suppression was mainly due to the pelvic RT, this study included rectal cancer patients only treated with capecitabine or continuous infusion 5-FU as part of the CRT regimen since these have similar toxicity (26) and mainly function as radiosensitizers (27,28). By including colon cancer patients treated with oxaliplatin in the adjuvant treatment period, we sought to control for the extent of expected chemotherapy induced BM injury to best ascertain the importance of dosimetric sparing during CRT.

There were some limitations to this study. Besides limitations inherent to retrospective analysis, there are limitations in that the effects of 5-FU versus capecitabine on the long-term function of pelvic BM are unknown, although evidence suggests they are mainly radiosensitizers. Since oxaliplatin is myelosuppressive, we did not include any rectal cancer patients treated during neoadjuvant CRT with oxaliplatin. Furthermore while bevacizumab does not cause added toxicity (14), there are no trials, which compare FOLFOX to CapeOX chemotherapy in the adjuvant setting in colorectal cancer since both are recommended agents (29). Ultimately though, the comparison with colon cancer patients created a control in this retrospective study and helped to better demonstrate the longer term effects of BM suppression during CRT in rectal cancer patients. Ideally, the rates of HT and the timing before experiencing HT should be evaluated in a prospective manner.

Conclusions

Rectal cancer patients are more likely to experience HT3 earlier than colon cancer patients. When presented with patients with rectal cancer who are likely to receive OxF based adjuvant chemotherapy, clinicians should consider sparing the PBM from radiation during preoperative neoadjuvant CRT which may make adjuvant chemotherapy more tolerable.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the institutional ethics board of Rutgers Cancer Institute of New Jersey (NO. Pro20140001136).

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