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ORIGINAL ARTICLE

FOLFOX chemotherapy can safely be given to neutropenic patients with early-stage colorectal cancer for higher dose intensity and fewer visits

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Abstract
Purpose How does giving adjuvant FOLFOX chemotherapy to patients with early-stage colorectal cancer (ESCRC) regardless of the day-before absolute neutrophil counts (ANC) effect chemotherapy-induced febrile neutropenia (CIFN) rates, received dose intensity (RDI), and chemotherapy cycle delay? Does an ANC level predict future neutropenia?
Methods A retrospective chart review was conducted on all patients receiving adjuvant chemotherapy for ESCRC at a mid-sized community hospital in Toronto, Ontario, Canada between April 2005 and May 2014. All patients were under one medical oncologist. Day-before CBC data were collected along with other patient characteristics. CIFN was confirmed by hospital records. Inclusion criteria were met by 132 patients. Overall, 1074 cycles of chemotherapy were analyzed.
Results Six episodes of CIFN were observed. There was a significant difference in the average day-before ANC between patients who developed CIFN (1.4×10^9/L, 95 % CI 0.76–2.0×10^9/L) and those who did not (2.9×10^9/L, 95 % CI 2.8–3.0×10^9/L, $p = 0.03$). The RDI for oxaliplatin was 0.95 and for 5-fluorouracil (5-FU) was 0.96. A total of 170 cycles were given at day-before ANC $<1.5 \times 10^9$/L (range 0.1×10^9/L–1.4×10^9/L), and 24 were delayed for 1 week for hematologic reasons. Cycles given with grade 2 neutropenia predicted higher grades of neutropenia with a sensitivity of 0.22 (95 % CI 0.12–0.38).
Conclusions Adjuvant FOLFOX chemotherapy may be given in the setting of low day-before ANC to patients with ESCRC. The benefits include higher RDI and a reduced number of clinic visits for the patient.

Keywords Colon cancer · Neutropenia · Febrile neutropenia · Dose intensity · Day-before bloodwork

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Introduction

Treatment of stage III and some stage II colorectal cancer with FOLFOX-type adjuvant chemotherapy improves survival [1]. FOLFOX has been associated with high rates of neutropenia, but low rates of chemotherapy-induced febrile neutropenia (CIFN) [1–3]. In many clinics, dose delays and dose reductions are instituted at an arbitrary absolute neutrophil count (ANC) to prevent hematologic complications [1, 4]. The MOSAIC strategy delays chemotherapy for up to 3 weeks until the ANC is $>1.5 \times 10^9$/L and dose reductions are introduced for subsequent cycles for ANC $<1.0 \times 10^9$/L [1]. This will reduce received dose intensity (RDI) and increase the total number of visits for patients.

A higher RDI has been associated with improved survival in many cancers [5, 6]. Myeloid growth factors are used to prevent dose modification which would adversely effect RDI [6]. There are conflicting data regarding the association of RDI and improved survival in the treatment of colorectal cancer as it has never been directly tested [7–9].

The ANC has long been used to regulate dosages of chemotherapy [10] and is typically used as such for FOLFOX-type chemotherapy [1]. Traditionally, an ANC $\geq 1.5 \times 10^9$/L has been used as a trigger for full-dose chemotherapy [11]. An ANC below this level usually requires a dose delay, dose

reduction, or the addition of growth factors [11]. However, recently, this traditional concept has been questioned [12, 13].

The use of full-dose chemotherapy at low day-before ANC, without dose-delay, or the use of myeloid growth factors has been looked at in the adjuvant breast cancer setting. This practice was not associated with an increased risk of CIFN and was associated with a high RDI [12]. However, a reliable marker for patients at risk for CIFN has not been determined, especially in the early-stage colorectal cancer (ESCRC) setting.

In many chemotherapy clinics, the CBC is drawn the day before the planned treatment. The chemotherapy order is then written for the next day based on those results. This two-visit system allows for the efficient use of chemotherapy clinic resources. However, no evidence-based guidelines for laboratory values are available with which to make the decision to allow full-dose chemotherapy in the adjuvant setting for ESCRC.

At our mid-size community hospital, a two-visit system is used. Adjuvant chemotherapy for ESCRC is routinely given when the day-before ANC is $<1.5 \times 10^9$/L without dose delay or growth factor use, with occasional removal of the 5-fluorouracil bolus as the only modification. This paper reviews the incidence of CIFN, RDI, and the number of clinic visits with this strategy. When the chemotherapy was given with grade 2 neutropenia [14], the ANC of the subsequent cycle was also examined.

Materials and methods

Study design and patient selection

A retrospective chart review was carried out for every patient who received adjuvant chemotherapy for ESCRC at Rouge Valley Centenary Hospital in Toronto, Ontario, Canada. All subjects were under the care of one medical oncologist (JAC) and received treatment from April 2005 to May 2014. Research Ethics Board approval was obtained.

Patients with pathologically confirmed colon or rectal cancer receiving adjuvant treatment for stages I to IIIC were included. Only cycles in which the CBC was drawn the day before treatment were analyzed for CIFN and dose delay. Both FOLFOX 4 (leucovorin 200 mg/m^2 intravenous (IV) then 5-fluorouracil (5-FU) 400 mg/m^2 followed by 600 mg/m^2 over 22 h, repeated for two consecutive days, and oxaliplatin 85 mg/m^2 IV on day 1) and mFOLFOX 6 (leucovorin 400 mg/m^2 IV on day 1, 5-FU 400 mg/m^2 on day 1 followed by 2400 mg/m^2 over 46 h, and oxaliplatin 85 mg/m^2 IV on day 1) were eligible. There was no protocol mandating chemotherapy dose delay, dose modification, or the use of granulocyte-colony stimulating factor (G-CSF) based on laboratory values. Chemotherapy proceeded at ANC $<1.5 \times 10^9$/L, based on the judgment of the oncologist (JAC) with no set lower limit employed. All chemotherapy doses, patient morphology data, and treatment dates were gathered for unadjusted RDI calculation [6]. The single RDI calculation for 5-FU included both the bolus and infusional components. The RDI calculation included all cycles that the patient received. All standard pathological prognostic factors; CBC, renal, and liver function tests; patient demographics; medications; comorbidities; ethnicity; smoking; alcohol usage; and incidence of diarrhea were collected.

All admissions to hospital for CIFN (ANC $<0.5 \times 10^9$/L and a single temperature >38 °C) [15] were captured and confirmed by hospital records.

Statistical methods

Demographic and clinical data were presented descriptively. Difference in the average day-before ANC between patients was compared using Student's *t* test. Statistical analyses were performed using Stata release 11.0 (Stata Corp., USA).

Results

Patient characteristics and treatment details

A total of 132 charts met the above criteria and were reviewed. Seventy-three percent of the charts were colon cancer (Table 1). Of the 1420 cycles available, 1074 met the inclusion criteria and were eligible for analysis. The median number of cycles included for analysis was 6 per patient. The maximum number of cycles for colon cancer patients was 12 and for rectal cancer patients was 8. The mean age was 62 years and 57 % of the patients were male. About 60 % were Caucasian. Fifty-four percent of the patients received mFOLFOX 6. There were no deaths.

CIFN events and ANC

Six patients developed CIFN for a rate of 4.5 % (95 % CI 1.7–9.6 %). A total of 170 cycles of chemotherapy were given at a day-before ANC $<1.5 \times 10^9$/L (range 0.1–1.4 $\times 10^9$/L). The six CIFNs occurred during cycles where the day-before ANC ($\times 10^9$/L) was 0.5, 1.2, 1.3, 1.4, 1.6, and 2.3. The CIFNs were at cycles 6, 3, 9, 7, 2, and 8, respectively. There was a significant difference in the average day-before ANC between patients who developed CIFN (1.4×10^9/L, 95 % CI 0.76–2.0×10^9/L) and those who did not (2.9×10^9/L, 95 % CI 2.8–3.0 $\times 10^9$/L, $p = 0.03$). Due to the low frequency of CIFN, the other gathered data could not be correlated to CIFN. Comparison to other studies is found in Table 2.

Table 1 Patient demographics, disease, and treatment characteristics

Characteristic	Number(%)
Mean age (years) (range)	62(37–84)
Sex	
Male	77(58)
Female	55(42)
Race	
Caucasian	79(60)
East Asian	31(23)
South Asian	10(8)
African Canadian	8(6)
South East Asian	4(3)
Primary	
Colon	97(73)
Rectal	35(27)
Stage	
I	1(1)
IIA	21(16)
IIB	8(6)
IIIA	29(22)
IIIB	68(51)
IIIC	5(4)
Chemotherapy programs	
FOLFOX4	60(46)
mFOLFOX6	72(54)

Received dose intensity

The RDI for oxaliplatin was 0.95 and for 5-fluorouracil was 0.96. The 5-FU bolus was eventually removed from 23 patients for hematologic toxicity, usually profound neutropenia. The RDI is compared to other studies (Table 2). The strategy of the other studies for dealing with low neutrophil and platelet counts was variable.

Neutropenia

Rates of grade 3/4 neutropenia [14] in the literature ranged from 29.4 to 62.1 %. In the current study, only data with day-before bloodwork were eligible, meaning that only an average of six cycles per patient were eligible for the 25.7 % observed.

Forty-four percent of patients had grades 2–4 neutropenia with 28 % experiencing multiple episodes of neutropenia. The maximum possible number of neutropenic episodes was 11, assuming a normal first-cycle ANC and 12 cycles of chemotherapy. One patient experienced the maximum number (Fig. 1). Thirty-four patients had multiple episodes of neutropenia without CIFN.

Treatment completion

Out of 132 patients, 108 completed all of the planned cycles. Twenty-one patients experienced at least one cycle delay for hematologic reasons. Out of a total of 1074 cycles, 24 were delayed for hematologic reasons. Of these, five were delayed by covering physicians, the balance were delayed for reasons of clinical judgment usually for marked hematologic toxicity. There was a positive association between age and dose delays where older patients were more likely to experience hematological toxicity compared to younger patients (OR = 1.05, $p = 0.018$).

In Table 3, the number of cycles given and held based on the day-before ANC and day-before platelet count is listed. This is in comparison to the MOSAIC strategy, which mandated cycle delay for an ANC less than 1.5×10^9/L and a platelet count of less than 100×10^9/L. The cumulative number of chemotherapy cycles given instead of delayed when MOSAIC strategies were used is also listed. A specific cycle was only counted once. When both counts were low, the cycle was listed with the higher-grade abnormality.

Table 2 Comparison of studies using adjuvant FOLFOX chemotherapy for ESCRC to current study

Study author, date	Number	Chemo	CIFN(%)	Strategy	Grade 3/4 (%)	RDI oxali	RDI 5-FU
André, 2004	2246	FOLFOX 4	1.8	MOSAIC	41.1	0.86	0.84
Allegra, 2009	2710	mFOLFOX6	1.7	Reduced grade 3/4	32.6	0.95	0.96
Jeon, 2011	82	FOLFOX4; mFOLFOX6	0	MOSAIC	40.2	NR	NR
Uncu, 2013	667	FOLFOX4; mFOLFOX4; FOLFOX6	2.7	Not stated	29.4	NR	NR
Kim, 2013	391	FOLFOX4	5.7, >65 years; 2.8, <65 years	MOSAIC	62.1; 46.5	0.76; 0.79	0.75; 0.80
Chu-Yuan, 2013	243	mFOLFOX6	1.6 at 5 cycles	15 % reduction	20.2	NR	NR
Smoragiewicz, 2014	114	mFOLFOX6	0	Not stated	38	0.81	0.85
Chiarotto, 2015	132	FOLFOX4; mFOLFOX6	4.5	See paper	25.7 for 6 cycles	0.95	0.96

N number of patients in study, *Chemo* chemotherapy, *Strategy* strategy for neutropenia dosing, *Grade* grade of neutropenia, *oxali* oxaliplatin, *NR* not reported

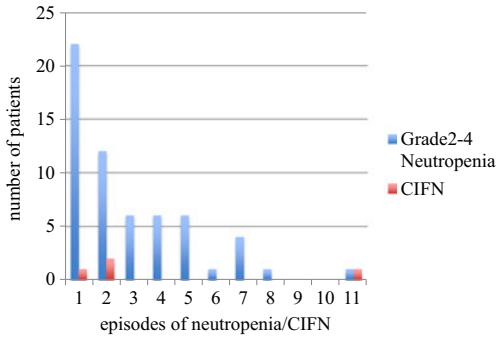

Fig. 1 Number of patients experiencing day-before neutropenia of various frequencies and episodes of CIFN associated with that frequency

Predictive value of grade 2 neutropenia

Cycles with grade 2 neutropenia (day-before ANC 1.0–1.49 × 10^9/L) [14] were examined to determine whether it predicted for higher grades of neutropenia. There were no dose modifications. Twenty-two percent of patients receiving chemotherapy with grade 2 neutropenia had grade 3/4 neutropenia (day-before ANC <1.0 × 10^9/L) in the subsequent cycle (Fig. 2). As a diagnostic test, the sensitivity of grade 2 neutropenia to predict grade 3/4 neutropenia in the next cycle was 0.22 (95 % CI 0.12–0.38), the specificity was 0.95 (95 % CI 0.93–0.96), positive predictive value (PPV) was 0.22 (95 % CI 0.12–0.37) and negative predictive value (NPV) was 0.95 (95 % CI 0.93–0.97). When patients received chemotherapy with grade 3/4 neutropenia, 63 % of patients had grades 0–2 neutropenia in the preceding cycle including 42 % of patients with grade 0/1 neutropenia (Fig. 3).

The mean ANC dropped with each subsequent cycle after the first cycle. The mean ANC with the first cycle was 5.0 × 10^9/L (95 % CI, 4.6–5.4 × 10^9/L). The mean day-before ANC fell progressively to 2.8 × 10^9/L (95 % CI, 2.5–3.1 × 10^9/L) at cycle 4, 2.4 × 10^9/L (95 % CI, 2.3–2.5 × 10^9/L) at cycle 8, and 2.0 × 10^9/L (95 % CI, 1.8–2.3 × 10^9/L) by the 12th cycle.

Discussion

One of the goals of this study was to determine whether administering FOLFOX-type chemotherapy with low day-before ANC increases the incidence of CIFN. The rate of CIFN for this study, 4.5 %, is at the high end of the range published in the literature (Table 2). The literature differed in the regimens used [16], the definition of CIFN [4], dose-reduction strategies, ethnic populations, and the use of myeloid growth factors [9].

There were not enough CIFN events to statistically correlate day-before ANC and subsequent occurrence of CIFN in this exploratory study. There was a statistical difference in the mean day-before ANC for those patients who experienced CIFN and those who did not. This may be suggestive of a correlation between low day-before ANC and subsequent CIFN. However, multiple other cycles were given at low

Table 3 Chemotherapy decision according to day-before ANC or day-before platelet count

Day-before ANC (×10^9/L)	Number of cycles chemo given	Number of cycles chemo held	Cumulative number of cycles given	Day-before platelet count (×10^9/L)	Number of cycles chemo given	Number of cycles chemo held	Cumulative number of cycles given
0	0	1	0	<39	1	0	1
0.1	2	3	2	40–49	5	3	6
0.2	1	5	3	50–59	7	0	13
0.3	5	4	8	60–69	5	1	18
0.4	2	2	10	70–79	17	2	35
0.5	7	0	17	80–89	32	0	67
0.6	9	0	26	90–99	32	1	99
0.7	11	2	37				
0.8	18	0	55				
0.9	16	0	71				
1.0	16	0	87				
1.1	17	0	104				
1.2	21	0	125				
1.3	25	0	150				
1.4	20	0	170				

A cycle is only counted once

Chemo chemotherapy

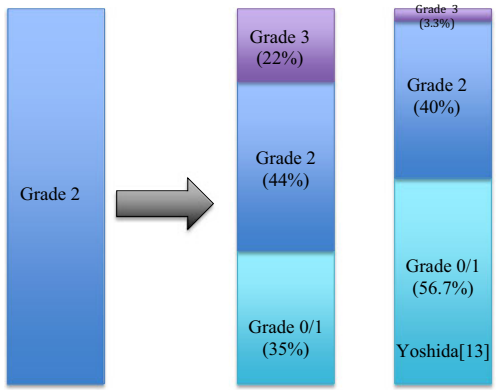

Fig. 2 Patients receiving chemotherapy with grade 2 neutropenia (*1st bar*) and the grade of neutropenia in the following cycle (*2nd bar*) in comparison to data from Yoshida et al. [13] (*3rd bar*)

ANC without incident. The current study showed a progressive fall in the ANC with each cycle of aggressively dosed chemotherapy. One hypothesis is that this difference may be a function of the cycle number of the CIFN.

None of the studies noted the ANC for the CIFN events (Table 2). Given the low rate of CIFN with the use of FOLFOX-type chemotherapy, an assessment of risk factors leading to this complication, including the ANC, would be difficult. As such, a direct correlation between ANC and CIFN risk has not been established. Yet, ANC continues to be used as a trigger for full-dose, on-time chemotherapy.

The use of an arbitrary ANC as a trigger for full-dose chemotherapy has recently been questioned [12, 13]. Most studies using FOLFOX-type chemotherapy require an ANC of at least 1.5×10^9/L to allow full-dose treatment [1]. Otherwise, the chemotherapy is delayed for at least 1 week and perhaps dose reduced for subsequent cycles. In practice, the trigger ANC is quite variable [11]. Chemotherapy dosing with little dependence on the ANC would allow for more on-time chemotherapy cycles and higher RDI.

Dose delay will reduce RDI. While RDI has been associated with improved survival in many tumor types [5, 6], increased RDI of FOLFOX chemotherapy in ESCRC has not proven survival benefit. Smoragiewicz et al. did not find a correlation in the adjuvant setting; however, they conducted a retrospective chart review without control for prognostic factors such as stage of disease [9]. Shitara et al. found survival was correlated with neutropenia after adjustment for prognostic factors using first-line FOLFOX in metastatic colon cancer [7]. Interestingly, they concluded that neutropenia might be a surrogate for RDI and that dose adjustments based on neutropenia should be reconsidered.

The RDI achieved in the current study is at the higher range of RDI documented in the literature (Table 2). Allegra et al. documented identical RDI and a much lower rate of CIFN, with a more conservative dosing strategy [3]. More typically, RDI using a MOSAIC-type dose modification is about 0.80.

Dose delay related to arbitrary lab levels delays treatment for patients. In the current study, 16 % (21/132) of patients experienced a cycle delay. This compares to 35.8 % for Uncu et al. [16] and a calculated 47 % for Smoragiewicz et al. [9] where dose reduction strategy was not specified. For the current study, a cumulative total of 170 cycles was given in the setting of neutropenia and 99 was given in the setting of thrombocytopenia for a total of 269 cycles (Table 3). This reduces the number of patient clinic visits while achieving higher RDI.

Chu-Yuan et al. found the mean ANC at cycle 1 to be 4.27×10^9/L (95 % CI, 4.1–4.5 $\times 10^9$/L) [8]. This compares to 5.0×10^9/L (95 % CI, 4.6–5.4 $\times 10^9$/L) for the current study. A progressive fall in the mean day-before ANC was recorded with each cycle of adjuvant chemotherapy, as has been reported previously [9].

FOLFOX-type chemotherapy has a low rate of CIFN but a significant rate of neutropenia. This makes it appropriate to test full-dose treatment with low ANC. XELOX was given to patients with metastatic colorectal cancer with grade 2 neutropenia [13]. CIFN was not increased. With Hodgkin lymphoma, the current standard of practice is to give appropriately selected patients ABVD regardless of the pretreatment ANC. This has not been associated with an increased rate of CIFN and/or mortality [17].

Dihydropyrimidine dehydrogenase deficiency causes neutropenia in FOLFOX-type chemotherapy [18]. This may explain observed neutropenia and CIFN. This study has shown that some patients tolerate low neutrophil counts repeatedly with no evidence of CIFN (Fig. 1). Other patients never experience pretreatment neutropenia. Dose delays for those with neutropenia who could tolerate chemotherapy would only compromise their treatment.

The CIFN events occurred at day-before ANCs of between 0.5×10^9/L and 2.3×10^9/L. There was one event at grade 0, one event at grade 1, three events at grade 2, and one event at grade 3. There is no way to translate these levels to an ANC

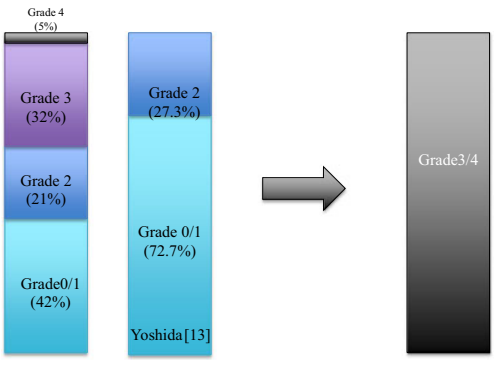

Fig. 3 Patients experiencing grade 3/4 neutropenia (*3rd bar*) and the grade of neutropenia in the preceding cycle (*1st bar*) in comparison to data from Yoshida et al. [13] (*2nd bar*). Note that for Yoshida et al., chemotherapy was delayed for grade 3/4 neutropenia

drawn the day of chemotherapy, and current neutropenia grades have no equivalent for day-before ANC.

The risk of CIFN related to day-before ANC should be a continuous variable [12] without a definite number separating low risk from high risk. However, no episodes of CIFN were observed at day-before ANC greater than 2.3×10^9/L. To use this as a standard, 477 cycles would have been dose delayed and/or dose reduced. This would have caused a marked reduction to RDI as well as a major inconvenience for both patients and the chemotherapy clinic.

Chemotherapy may not be given at low ANC due to concerns of progressive hematologic compromise with unregulated use of chemotherapy. Yoshida et al. tested grade 2 neutropenia as a marker for grade 3 neutropenia in metastatic colon cancer using XELOX [13]. Chemotherapy was used with grade 2 neutropenia and discontinued for grade 3/4 neutropenia. Figure 2 shows the resulting neutropenia grades from the current study compared to Yoshida et al. The differences are partly due to the different chemotherapy regimens [2] and the day-before CBC data for the current study. Figure 3 shows the grade of neutropenia in the cycle before those with grade 3/4 neutropenia. Yoshida et al. deferred chemotherapy in the setting of grade 3/4 neutropenia. They concluded that grade 2 neutropenia could not predict for grade 3 neutropenia. In the current study, the sensitivity and PPV is sufficiently low to support Yoshida et al's findings. The specificity and NPV for grade 2 neutropenia to predict grade 3 is quite high, indicating that a cycle with grade 0/1 neutropenia is very unlikely to proceed to grade 3/4 in the next cycle.

Aggressive dosing may reduce the rate of regimen completion due to chemotherapy complication. However, the completion rate in the current study was 82 %, which compares to 91 % [8] and 75 % [9] in other studies.

Conclusion

It has been a standard practice for medical oncologists to use a pre-defined set of lab values to determine the use of full-dose chemotherapy. As this study has shown, no one value can be applied to all patients. An arbitrary lab value will result in unnecessary dose delays, reduced RDI and more visits for patients. FOLFOX chemotherapy given without dose modification in grade 2 neutropenia is most likely associated with the same grade or less in the next cycle. This study has shown that many patients can tolerate chemotherapy while neutropenic, especially with the 5-FU bolus removed. Additionally, the use of myeloid growth factors may not be necessary in this patient population.

Characteristics that identify risk factors for CIFN were unable to be defined by this study due to the low incidence of CIFN. More work needs to be done to give medical oncologists a validated set of lab values to help to confidently decide the use of full-dose, on-time chemotherapy in the best interests of the patient.

Future work may be to invite other facilities to replicate this work to enlarge the database and compare results for similarities and differences.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest relevant to the conduct of this study. The authors have full control of the data, which may be reviewed by the journal upon request.

Disclosures None

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