Delivery of Adjuvant Oxaliplatin for Colon Cancer: Insights From Routine Clinical Practice

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Abstract

Background: Adjuvant oxaliplatin is now a standard treatment option for patients with early-stage colon cancer. However, treatment delivery and outcomes achieved in routine practice are not well described. **Methods:** All cases of colon cancer diagnosed in Ontario from 2002 to 2008 were identified using the Ontario Cancer Registry. Pathology reports were obtained for a 25% random sample to identify stage II and III cases; patients treated with adjuvant oxaliplatin were included in this analysis. Treatment records were reviewed to identify oxaliplatin dose reductions or omissions. Modified Poisson regression was used to evaluate factors associated with dose reduction/omission. Cox proportional hazards model was used to explore factors associated with cancer-specific survival (CSS) and overall survival (OS). **Results:** The study population included 532 patients; 88% (469/532) had stage III disease. The mean/median number of oxaliplatin cycles delivered was 10/12. A dose reduction/omission of oxaliplatin occurred in 54% of cases (288/532), and the dose was subsequently escalated in 34% of these (97/288). Women were more likely than men to have dose reduction/omission (relative risk, 1.29; 95% CI, 1.10–1.51). Dose reduction/omission was not associated with inferior CSS (hazard ratio [HR], 0.76; 95% CI, 0.51–1.14) or OS (HR, 0.81; 95% CI, 0.59–1.13). Five-year CSS and OS of all cases were 77% (95% CI, 72–81) and 72% (95% CI, 68–76), respectively. On-treatment mortality rates were 1% and 3% within 30 and 90 days of oxaliplatin, respectively. **Conclusions:** Dose reductions of adjuvant oxaliplatin are common in routine practice but are not associated with inferior survival. Long-term survival achieved in the general population is comparable to the results of clinical trials.

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Background

Adjuvant chemotherapy (ACT) with 5-fluorouracil (FU) has been the standard of care for stage III or high-risk stage II colon cancer since the 1990s.¹ This treatment is based on a series of randomized clinical trials (RCTs) showing a 30% reduction in death, translating into an absolute improvement in 5-year overall survival (OS) of 10% to 25%.² Oral capecitabine is known to offer com-

parable efficacy and is often substituted for intravenous 5-FU.³ In 2004, the pivotal MOSIAC trial demonstrated that the addition of oxaliplatin to 5-FU (FOLFOX) led to improved disease-free survival.⁴ Similar findings were observed in a second RCT.⁵ Updated analyses of the MOSIAC trial demonstrated oxaliplatin is associated with improved survival at 10 years (72% vs 67%; $P=.043$).⁵ Accordingly, the standard of care for patients with stage

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Dr. Booth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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III and high-risk stage II colon cancer includes ACT with 5-FU/capecitabine with or without oxaliplatin.^{6,7}

It is well-known that efficacy observed in clinical trials may not translate into effectiveness in the general population.^{8,9} This may relate to suboptimal adoption of new therapies in clinical practice. It may also relate to the fact that patients, providers, and health systems differ considerably between high-volume specialized centers that conduct trials and routine practice.¹⁰ Population-based outcome studies are useful to describe practice and outcomes achieved in the real world.^{11,12} Although a number of studies have previously reported rates of ACT use in colon cancer in routine clinical practice,^{13–15} there is limited literature describing details of how oxaliplatin is delivered in routine practice.

Knowledge of oxaliplatin delivery in routine practice comes from a handful of small population-based studies (sample size, 114–281 patients).^{16–18} From these studies it is clear that a substantial proportion of patients will have a dose reduction in oxaliplatin. Whether dose reductions of oxaliplatin compromise long-term outcomes remains unclear, with conflicting results reported by 2 small studies.^{17,18} OS at 5 years has been reported as 70% and 78%, but these reports had 114 and 182 oxaliplatin cases, respectively.^{17,18} In a single study, mortality within 60 days of starting adjuvant oxaliplatin was reported as 1% to 2%.¹⁹ In the pivotal MOSAIC trial, OS at 5 years was closer to 80% and treatment-related mortality was less than 1%.^{4,20}

Given the gaps in existing knowledge, we undertook a population-based study to describe the delivery of oxaliplatin ACT for colon cancer in Ontario. The study objectives were to (1) describe delivery of oxaliplatin in routine practice; (2) identify factors associated with dose reduction; and (3) explore survival outcomes associated with oxaliplatin-based ACT in routine practice and whether dose reductions are associated with inferior survival.

Methods

Study Design and Population

This is a secondary analysis of a population-based, retrospective cohort study to describe the management and outcome of resected stage II and III colon cancer in the Canadian province of Ontario. The primary results and study cohort were recently re-

ported.²¹ Ontario has a population of approximately 13.5 million and a single-payer universal health insurance program. The study population included patients who underwent resection of stage II and III colon cancer in Ontario between 2002 and 2008. To identify the study cohort, we used the Ontario Cancer Registry (OCR) to identify all incident cases of colorectal cancer (CRC) in Ontario diagnosed in 2000 to 2008. The OCR does not capture disease stage for all patients; therefore, we obtained surgical pathology reports for a random sample of 25% of cases. Reports were not available for patients who underwent surgery in 2005; as such, the study cohort is restricted to patients who had surgery in 2002 to 2004 and 2006 to 2008. The study was approved by the Research Ethics Board of Queen's University.

Data Sources and Linkage

The OCR is a passive, population-based cancer registry that captures diagnostic and demographic information on at least 98% of all incident cases of cancer in the province of Ontario.²² The OCR also provides information about vital status and cause of death. Records of hospitalization from the Canadian Institute for Health Information (CIHI) provided information about surgical procedures; these records are known to have a very high level of completeness for CRC surgery.²³ Provincial physician billing records from the Ontario Health Insurance Plan, treatment records from regional cancer centers, and provincial records of the New Drug Funding Program were used to identify chemotherapy use. A team of trained data abstractors reviewed the pathology reports and entered information about extent of disease into an electronic database.

Measures and Outcomes

Indicators of the socioeconomic status of the community in which patients resided at diagnosis were linked as described previously.²⁴ Q1 represents the communities where the poorest 20% of the Ontario population resided. Geographic regions reflect the catchment areas for Ontario's regional cancer centers. Comorbidity was classified using the Charlson index modified for administrative data based on all noncancer diagnoses recorded during any hospital admission within 5 years before surgery.²⁵

ACT was defined as chemotherapy initiated within 16 weeks after surgery. Drug delivery records

were reviewed to identify cases treated with oxaliplatin. Cases also treated with 5-FU were classified as FOLFOX and cases with associated records of capecitabine were classified as CAPOX. Because oxaliplatin was reimbursed by the New Drug Funding Program, there were some cases in which oxaliplatin was identified but the concomitant chemotherapy (ie, 5-FU or capecitabine) was not known. Oxaliplatin dose reduction was defined as the delivery of any dose of oxaliplatin that was less than the initial dose. Cases with a treatment record showing the delivery of a fluoropyrimidine without oxaliplatin were classified as having a dose omission.

Cancer-specific survival (CSS) and OS were determined from date of surgery. To account for possible cause-of-death miscoding, CSS included death from any cancer. Complete information about vital status in the OCR was available up to December 31, 2012; cause of death was available up to December 31, 2010.

Statistical Analysis

Comparisons of proportions between study groups were made using the chi-square test. Survival was determined from date of surgery using the Kaplan-Meier technique and comparisons between groups were made using the log-rank test. Factors associated with dose reduction/omission were evaluated using modified Poisson regression. The association between patient-, disease-, and treatment-related factors with OS/CSS was evaluated using the Cox proportional hazards regression model. Results were considered statistically significant at a *P* value of less than 0.05. All analyses were performed using SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Study Population

Among the 5,519 patients with stage II and III colon cancer, 42% received ACT. A specific ACT regimen was identified for 67% cases; among these cases, oxaliplatin was delivered to 35%. A total of 547 cases were treated with oxaliplatin within 16 weeks of surgery; 97% (532/547) had 12 or fewer cycles and 3% (15/547) had more than 12 cycles. Because it was not clear whether the cases with more than 12 cycles received ACT or palliative chemotherapy, they were excluded from the analysis. The study population therefore includes 532 cases. Characteristics of the

study population are shown in Table 1. The median age was 61 years and 54% (289/532) were male; 88% (469/532) of cases had stage III disease. Among the 63 patients with stage II disease, 27% (17/63) had T4 tumors, 13% (8/63) had fewer than 12 lymph nodes resected, 27% (17/63) had lymphovascular invasion, and 21% (13/63) had poorly differentiated histology. Among the 532 patients treated with oxaliplatin,

Table 1. Characteristics of Patients With Colon Cancer Treated With Adjuvant Chemotherapy

N (%)	
Patient-related	
Age, y	
20–49	75 (14%)
50–59	147 (28%)
60–69	208 (39%)
≥70	102 (19%)
Sex	
Male	289 (54%)
Female	243 (46%)
SES by quintile ^a	
1	90 (17%)
2	111 (21%)
3	128 (24%)
4	90 (17%)
5	113 (21%)
Charlson comorbidity score	
0	475 (89%)
1	37 (7%)
≥2	20 (4%)
Disease-related	
Histology, lymphovascular invasion	
Yes	249 (47%)
No	264 (50%)
NA	19 (4%)
N stage	
0	63 (12%)
1	251 (47%)
2	218 (41%)
T stage	
≤1	8 (2%)
2	36 (7%)
3	343 (64%)
4	145 (27%)
Grade	
Well to moderately differentiated	419 (79%)
Poorly differentiated	107 (20%)
Unstated	6 (1%)
Concomitant chemotherapy	
5-FU (FOLFOX)	397 (75%)
Capecitabine (CAPOX)	26 (5%)
Unknown	109 (20%)

Abbreviations: NA, not applicable; SES, socioeconomic status.
^aQuintile 1 represents the communities where the poorest 20% of the Ontario population resided.

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we were able to identify concomitant use of intravenous 5-FU in 75% (397/532) and concomitant capecitabine in 5% (26/532). The remaining 20% of cases (109/532) received oxaliplatin but we were unable to identify whether it was delivered with 5-FU or capecitabine.

Chemotherapy Delivery

The mean number of oxaliplatin cycles was 10. Half of the cases (269/532; 51%) received 12 cycles of oxaliplatin. Oxaliplatin dose was reduced or omitted in 54% of cases (288/532); in 34% of these cases (97/288), oxaliplatin was subsequently reintroduced and/or dose-escalated.

Factors associated with dose reduction/omission are shown in Table 2. Age, comorbidity, and extent of disease were not associated with dose reduction/omission. However, women were substantially more likely than men to have a dose reduction/omission (61% vs 48%; $P=.002$); this persisted on multivariate analysis (relative risk [RR], 1.29; 95% CI, 1.10–1.51).

Outcomes

Death rates within 30 and 90 days of any dose of oxaliplatin were 1% (7/532) and 3% (16/532), respectively. The 5-year CSS and OS rates of all cases were 77% (95% CI, 72–81) and 72% (95% CI, 68–76), respectively. As shown in Table 3, factors associated with inferior survival include advanced age, lymphovascular invasion, and poorly differentiated histology. Oxaliplatin dose reduction/omission was not associated with inferior CSS (hazard ratio [HR], 0.76; 95% CI, 0.51–1.14) or OS (HR, 0.81; 95% CI, 0.59–1.13).

Discussion

This population-based study describes the delivery of adjuvant oxaliplatin for stage II and III colon cancer in routine clinical practice. This is the largest such study in the literature and has several important findings. First, dose reduction/omission of oxaliplatin is common, occurring in approximately half of patients in routine practice. The dose will be subsequently increased in one-third of these cases. Second, we have found that dose reduction/omission is considerably more common in women compared with men. The reasons for this are not clear. Third, our data suggest that oxaliplatin dose reduction/omission is not associated with inferior long-term survival. Finally, long-

Table 2. Factors Associated With Oxaliplatin Dose Reduction in Patients With Colon Cancer Treated With Adjuvant Chemotherapy in Ontario 2002–2008 (n=532)

	Cases With Dose Reduction	Multivariate Analysis	
		RR (95% CI)	P Value
<i>Patient-related</i>			
Age, y			.275
20–49	45%	Ref	
50–59	56%	1.26 (0.94–1.69)	
60–69	57%	1.30 (0.98–1.73)	
≥70	51%	1.19 (0.85–1.65)	
Sex			.002
Male	48%	Ref	
Female	61%	1.29 (1.10–1.51)	
SES by quintile ^a			.339
1	50%	0.88 (0.68–1.13)	
2	59%	1.01 (0.81–1.25)	
3	52%	0.94 (0.74–1.19)	
4	48%	0.79 (0.61–1.03)	
5	60%	Ref	
Charlson comorbidity score			.785
0	55%	Ref	
≥1	51%	0.96 (0.72–1.28)	
<i>Disease-related</i>			
Histology, LVI ^b			.824
Yes	55%	1.02 (0.87–1.20)	
No	54%	Ref	
N stage			.940
Negative	54%	Ref	
Positive	54%	1.01 (0.78–1.31)	
T stage			.719
T<3	57%	Ref	
T3	53%	0.93 (0.71–1.23)	
T4	57%	1.00 (0.74–1.34)	
Grade ^c			.825
Well to moderately differentiated	54%	Ref	
Poorly differentiated	54%	1.02 (0.84–1.24)	
<i>Treatment-related</i>			
Geographic region			.184
A	55%	Ref	
B	61%	1.13 (0.90–1.42)	
C	67%	1.28 (1.02–1.61)	
D	46%	0.86 (0.55–1.34)	
E	45%	0.92 (0.56–1.53)	
F	67%	1.23 (0.75–2.02)	
G	41%	0.73 (0.47–1.15)	
H	48%	0.93 (0.72–1.20)	

Abbreviations: LVI, lymphovascular invasion; Ref, referent; RR, relative risk; SES, socioeconomic status.

^aQuintile 1 represents the communities where the poorest 20% of the Ontario population resided.

^b19 patients with unstated LVI were excluded from the analysis.

^c<6 patients with unstated grade were excluded from the analysis.

Characteristic	CSS			OS		
	5-y CSS	Multivariate Analysis HR (95% CI)	P Value	5-y OS	Multivariate Analysis HR (95% CI)	P Value
Patient-related						
Age, y			.003			.002
20–49 (n=75)	88%	Ref		82%	Ref	
50–59 (n=147)	77%	1.79 (0.79–4.09)		76%	1.81 (0.93–3.51)	
60–69 (n=208)	79%	2.50 (1.15–5.45)		71%	2.31 (1.23–4.33)	
≥70 (n=102)	59%	4.19 (1.83–9.60)		61%	3.42 (1.75–6.68)	
Sex			.926			.861
Male (n=289)	76%	Ref		73%	Ref	
Female (n=243)	76%	1.02 (0.68–1.54)		71%	0.97 (0.70–1.35)	
Charlson comorbidity score			.211			.249
0 (n=475)	78%	Ref		74%	Ref	
1+ (n=57)	NA ^a	1.43 (0.82–2.51)		60%	1.32 (0.82–2.12)	
Disease-related						
T stage			.244			.080
<T3 (n=44)	89%	Ref		86%	Ref	
T3 (n=343)	78%	2.44 (0.76–7.87)		73%	2.70 (1.10–6.68)	
T4 (n=145)	70%	2.77 (0.84–9.13)		66%	2.89 (1.14–7.30)	
N stage			.078			.687
Negative (n=63)	80%	Ref		78%	Ref	
Positive (n=469)	76%	0.57 (0.31–1.06)		71%	0.89 (0.51–1.55)	
LVI ^b			.001			<.001
Yes (n=249)	67%	2.08 (1.32–3.27)		64%	1.88 (1.33–2.67)	
No (n=264)	85%	Ref		80%	Ref	
Grade ^c			<.001			.010
Well to moderately differentiated (n=419)	81%	Ref		74%	Ref	
Poorly differentiated (n=107)	61%	2.58 (1.67–4.00)		63%	1.65 (1.13–2.42)	
Oxaliplatin dose reduction			.184			.221
Yes (n=288)	76%	0.76 (0.51–1.14)		73%	0.81 (0.59–1.13)	
No (n=244)	79%	Ref		71%	Ref	

Abbreviations: CSS, cancer-specific survival; HR, hazard ratio; LVI, lymphovascular invasion; NA, not applicable; OS, overall survival; Ref, referent.

^a5-year CSS cannot be calculated for this subgroup due to the low number of CSS events.

^b19 patients with unstated LVI were excluded from the analysis.

^c<6 patients with unstated grade were excluded from the analysis.

term survival of patients in routine practice is comparable to that seen in the relevant clinical trials.

It is worth considering the results of our study in light of the relevant clinical trials. The MOSAIC trial randomized 2,246 patients with stage II or III colon cancer to 12 cycles of FOLFOX or infusional 5-FU; 75% of patients received 12 cycles of oxaliplatin. The initial report in 2004 demonstrated improved disease-free survival.⁴ Longer-term analyses confirmed that this translated into a clinically meaningful difference in OS.²⁰ The NSABP CO7 trial has

shown that FLOX (a slightly different oxaliplatin-based regimen) improved disease-free survival.⁵ An updated analysis in 2011 did not yet show evidence of improved OS.²⁶

We are aware of several other reports that describe delivery of adjuvant oxaliplatin for colon cancer in routine practice. Sanoff et al^{14,19} published 2 studies using registry data from the United States. They found evidence of superior effectiveness of FOLFOX compared with 5-FU monotherapy among patients older than 75 years.¹⁴ They also found evi-

dence of greater toxicity compared with 5-FU.¹⁹ These studies do not describe long-term survival or details related to dose reduction or number of cycles. The authors attributed deaths that occurred between 30 and 90 days after surgery to chemotherapy; 1% to 2% of cases died within this period.

We are aware of 3 studies that have described details of adjuvant oxaliplatin delivery in routine practice. Using a population-based registry in the Netherlands, van Gils et al¹⁶ described the delivery of ACT to 391 patients with stage III colon cancer; oxaliplatin was delivered in 281 cases. Details pertaining to dose intensity were available for 102 cases. The authors reported that the median number of cycles was 12 for FOLFOX and 7 for CAPOX. Fifty percent of cases received a full course of treatment. Up to 70% of patients required a dose reduction or interruption in the delivery of oxaliplatin. Our own results are consistent with these findings. Aspinall et al¹⁷ reported a similar study using data from Veteran Affairs hospitals in the United States. They identified 182 patients who received oxaliplatin. Consistent with the results from our study and that of van Gils et al,¹⁶ 53% of patients received a full course of oxaliplatin, and dose reductions were common. However, contrary to our findings, Aspinall et al¹⁷ found that dose reductions were associated with inferior OS and disease-free survival. In a third study, Smoragiewicz et al¹⁸ identified 114 patients with stage II or III colon cancer treated with FOLFOX in British Columbia, Canada. Their findings are consistent with ours: the median number of cycles completed was 12, and 42% of cases received a dose reduction of oxaliplatin. In their analysis, dose reductions were not associated with inferior OS or relapse-free survival.

Our data provide insight into outcomes achieved with adjuvant oxaliplatin in routine clinical practice. Our observed rate of OS at 5 years (72%) is comparable to rates seen in other population-based reports (70% and 78%)^{17,18} and the MOSAIC trial (approximately 80%).²⁰ On-treatment mortality rates (1% within 30 days and 3% within 90 days) are also comparable to rates seen in the MOSAIC (0.5% within 30 days of oxaliplatin) and NSABP CO7 (1.4% within 60 days of oxaliplatin) clinical trials.^{4,5}

One unexpected finding that emerged from our study was the substantially greater rate of dose reduction/omission in women compared with men. To

our knowledge, this has not been previously reported in other trials of CRC. Our data do not provide insight into the causal mechanism for this observation. However, evidence suggests that women are more likely to develop 5-FU toxicity^{27,28} and oxaliplatin hypersensitivity.²⁹

Although our study provides detailed data regarding delivery of adjuvant oxaliplatin in routine clinical practice, several methodologic limitations merit comment. The study population was identified using linked administrative health databases. Although the OCR and the CIHI data sets are known to be consistent and complete,^{22,23} it is possible that our results may be biased by misclassification. Although the electronic data sources used in this study describe general aspects of disease, treatment, and outcome for all patients in the province, detailed information related to carcinoembryonic antigen level, toxicity, reason for dose reduction/omission, and performance status is not available and limits our analysis. Importantly, body surface area was not available, and for this reason we were not able to determine relative dose intensity. The existing data sets did not allow us to identify whether oxaliplatin was delivered with intravenous 5-FU or oral capecitabine in 20% of cases. Finally, as with any retrospective cohort study, our analysis evaluating whether dose reduction/omission is associated with reduced survival is vulnerable to residual confounding.

Our study population was identified from the OCR and is therefore unselected and includes patients of all ages. Our study is considerably larger than previously reported studies and is one of the only studies that is truly population-based. Because of the work required to manually review surgical pathology reports, our study population is a random sample of approximately 25% of all cases treated in Ontario during the study period. No substantial differences were seen between the randomly selected cases and the cases not included in our study population (see supplemental eTable 1 and eFigure 1, available with this article at JNCCN.org). We did not obtain pathology reports for cases who underwent surgery in 2005. We feel it is very unlikely that this would bias our results in any significant way. Finally, the current study does not address the gap between observed ACT use rates in routine care and optimal treatment rates. This issue is explored in greater detail in an earlier report by our group.²¹

Conclusions

Our results suggest that dose reductions/omissions of adjuvant oxaliplatin for colon cancer are common in routine clinical practice and are more likely in women compared with men. Our data do not show any signal that dose reduction/omission leads to inferior survival. Long-term survival of patients in routine practice is comparable to results observed in clinical trials.

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