Original Study

Safety and Effectiveness of Oxaliplatin-Based Chemotherapy Regimens in Adults 75 Years and Older With Colorectal Cancer

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Abstract

Although the safety and efficacy of oxaliplatin-based chemotherapy regimens for colorectal cancer (CRC) have been demonstrated in adults ≥ 75 years of age enrolled in clinical trials, safety and effectiveness outside the trial setting are less established. In this comparative effectiveness study, we note that older adults with stage III and metastatic CRC treated outside of a clinical trial experienced safety and effectiveness of oxaliplatin-based chemotherapy regimens comparable to that of younger adults.

Background: Although the safety and efficacy of oxaliplatin-based chemotherapy regimens for colorectal cancer (CRC) have been demonstrated in adults ≥ 75 years of age who are enrolled in clinical trials, safety and effectiveness outside the trial setting are less established. **Methods:** We retrospectively collected cases of patients ≥ 75 years of age who were diagnosed with stage III and metastatic CRC and initiated treatment between January 2000 and January 2007 at 2 academic hospitals in Boston, MA. Cases were matched in a 1:2 ratio to controls who were < 75 years of age by hospital site, stage of disease (stage III vs. metastatic) and line of therapy (first- or second-line or beyond). The primary study endpoints were grade ≥ 3 treatment-associated toxicities and intolerance (number of dose delays/reductions and hospital/facility admissions during treatment). The secondary endpoint was overall survival. **Results:** We identified 84 patients ≥ 75 years of age (25% ≥ 80 years) and 168 controls. In the cohort, 77% had colon cancer, 75% had metastatic disease, and 60% were receiving oxaliplatin as first-line therapy. There was no significant difference in grade ≥ 3 treatment-associated toxicities between the patients and the controls (71.4% vs. 68.5%, respectively; $P = .63$). Further there was no statistically significant difference between patients and controls for combined endpoints of any grade ≥ 3 toxicity or hospital/facility admission ($P = .92$). With a median follow-up of 52 months, 2-year overall survival was similar between patients and controls (43% vs. 52%, respectively; $P = .87$). **Conclusion:** Older adults with stage III and metastatic CRC treated outside of a clinical trial experienced safety and effectiveness of oxaliplatin-based chemotherapy regimens that was comparable to that of younger adults.

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Introduction

Colorectal cancer (CRC) accounts for approximately 10% of all new cancer cases and cancer-related deaths in the United States.[1] The incidence and prevalence of CRC is expected to continue to rise with advancing age.[1-3] Older adults are disproportionately affected by toxicity or suboptimal care when compared with their younger counterparts.[2-9] Oxaliplatin-based chemotherapy is the standard of care in the adjuvant setting for stage III disease and a standard first-line

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treatment option in the metastatic setting, yet many older adults do not receive the indicated chemotherapy.[1,2]

Most studies on treatment tolerance and efficacy in the elderly use pooled data to overcome the limited enrollment of older adults to clinical trials. However, such analyses may still have limited generalizability because disproportionately few older patients are enrolled in clinical trials.[4-6,10,11] Given that the median age of diagnosis for CRC is 69 years,[12] evaluation of the effectiveness and tolerance of oxaliplatin-based chemotherapy in older adults in a nonclinical trial population is warranted.

The objective of this case-control study was to compare the proportion of individuals at least 75 years of age with pathologic stage III and metastatic CRC experiencing intolerance or toxicity to oxaliplatin-based chemotherapy regimens to that of individuals younger than 75 years in a nonclinical trial cohort at 2 National Cancer Institute centers.

Patients and Methods

Study Design and Patient Selection

This case-control study used medical record review of 252 adults initiating oxaliplatin-based chemotherapy from January 1, 2000 to January 1, 2007 at Massachusetts General Hospital and Dana-Farber Cancer Institute, Boston, MA. We retrospectively collected cases of adults ≥ 75 years of age who were diagnosed with pathologic stage III and metastatic colon or rectal adenocarcinoma, matched to controls < 75 years of age by hospital site, stage of disease (stage III vs. metastatic), and line of therapy (first vs. second or beyond). After approval from the institutional review board, data on patient characteristics as well as disease and treatment characteristics of cases and controls were obtained by medical record review of the longitudinal medical record. Patient characteristics included age at onset of therapy, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), body mass index, number of medications, and number and type of comorbid medical conditions (CMCs). Disease and treatment characteristics included diagnosis, stage, type of oxaliplatin therapy, line of therapy, oncologist, number of dose reductions/delays, number of hospital/facility admissions, presence of grade ≥ 3 treatment-related toxicity, and reason for oxaliplatin discontinuation.

Study Endpoints

The primary study endpoints were proportion of patients experiencing grade ≥ 3 toxicities after initiation of oxaliplatin-based chemotherapy compared with matched controls and measures of intolerance to therapy. Intolerance is a measure of number of (1) dose delays (delay of scheduled treatment dose), (2) dose reductions, and (3) hospital/facility admissions during the treatment period. Toxicity reflects all grade ≥ 3 treatment-related toxicities documented in the electronic medical record during the treatment period. Toxicity was defined as grade ≥ 3 if it met Common Terminology Criteria for Adverse Events, version 3, criteria or if it resulted in termination of therapy. We also examined overall survival and the impact of the presence of CMC on rates of intolerance and toxicity. The CMCs measured included cardiac comorbidity (congestive heart failure, coronary artery disease, hypertension), endocrine comorbidity (diabetes mellitus, hypothyroidism, hyperthyroidism), neurologic comorbidity (neuropathy, cerebrovascular accident), psychiatric comorbidity (depression, bipolar disorder), pulmonary comorbidity (asthma, chronic obstructive pulmonary disease), renal comorbidity (chronic kidney disease), vascular comorbidity (venothromboembolic disease), and other cancers. The number of medications evaluated does not include those prescribed as adjuncts to chemotherapy (eg, antiemetic agents, stool softeners, or antidiarrheal medications).

Statistical Considerations

Data analysis consisted of comparative analyses using the χ^2 test for binary comparisons of toxicity and specific comorbid conditions (except renal disease for which the Fisher exact P value was reported because of low incidence). Kruskal-Wallis and Wilcoxon P values were reported for comparison of medians and means, respectively.

In the exploratory analysis, conditional logistic regression (conditioned on the matched cohort) was performed to determine the association between CMCs and medications and each individual measure of intolerance and rates of ≥ grade 3 toxicity. The Kaplan-Meier method and stratified log-rank tests were used to compare the overall survival of cases vs. controls. Since toxicity occurrence dates were not always available because of the retrospective nature of this study, conditional logistic regression was performed for overall survival at 1, 2, and 3 years from the date of the initial visit or first oxaliplatin use. Patients whose follow-up was less than the analysis-specified time point (1, 2, or 3 years) and who were still alive at last contact were excluded from the respective survival analysis. Patients who died were included in all 3 analyses, regardless of their survival times. Two hundred thirty-two patients was included in the 1-year analysis, 221 patients in the 2-year analysis, and 216 patients in the 3-year analysis.

Results

Patient Enrollment and Characteristics

The analysis cohort consisted of 252 adults (84 cases ≥ 75 years of age and 168 matched controls < 75 years of age). Twenty-five percent of the patients were ≥ 80 years at the time of diagnosis. The majority of patients were diagnosed with colon cancer (cases = 84%). More than two thirds of patients (77% of stage III and 77% of patients with metastases) received intravenous infusional 5-fluorouracil (5-FU) and leucovorin (5-FU/LV) with oxaliplatin (FOLFOX) as opposed to alternative regimens (single-agent oxaliplatin, bolus 5-FU, and leucovorin with oxaliplatin [FLOX]), or capecitabine with oxaliplatin (CAPOX)]. The proportion of patients receiving FOLFOX without bevacizumab in the metastatic setting (57/124 [46%] controls and 13/65 [20%] cases] partially reflects the fact that this study included patients treated before US Food and Drug Administration approval of bevacizumab in metastatic CRC in 2004.

The cohort is well matched by hospital site, stage, and line of therapy. The distributions of patient and tumor characteristics are similar between the cases and the controls (Table 1). Compared with controls, patients ≥ 75 years of age had a greater mean number of comorbid conditions (cases, 1.5; controls, 1.0; $P \leq .001$) and medications (cases, 4.8; controls, 3.3; $P \leq .001$). Evaluation of each comorbid condition reveals comparable distribution by age, with the exception of adults ≥ 75 years of age having a statistically significant greater number of cardiac comorbidities than their younger counterparts (57% cases vs. 33% controls; $P \leq .001$).

Table 1 Patient Distribution and Characteristics

Characteristic	Cases (n = 84)		Controls (n = 168)		*P* Value
	No.	%	No.	%	
Sex					
Female	38	45.2	82	48.8	.53
Male	46	54.8	86	51.2	
ECOG Performance Status					
0	11	29.7	11	29.7	.06
1	22	59.5	22	59.5	
2+	4	10.8	4	10.8	
Diagnosis					
Colon	71	84.5	124	73.8	.06
Rectum	13	15.5	44	26.2	
Stage					
III	18	21.4	44	26.2	.27
IV/metastatic	65	77.4	124	73.8	
Oxaliplatin Regimen					
Oxaliplatin Monotherapy[a]	18	21.4	8	4.8	<.001
FOLFOX[b]	60	71.4	146	86.9	
CAPOX[c]	5	6.0	14	8.3	
FLOX	1	1.2	0	0.0	
Line of Therapy					
First Line	50	59.5	100	59.5	1.00
Second Line And Beyond	34	40.5	68	40.5	
BMI (mean, range)	26.2 (14.2-37.1)		27.2 (17.7-53.1)		.23*
Number of Medications (mean, range)	4.8, 0-16		3.2, 0-13		<.001*
Number of Comorbid Medical Conditions (mean, range)	1.5, 0-5		0.9, 0-4		<.001*
Comorbid Medical Condition					
Pulmonary	8	9.5	11	6.5	.40
Cardiac	48	57.1	58	34.5	<.001
Vascular	10	11.9	8	4.8	.04
Renal	4	4.8	1	0.6	.03
Endocrine	24	28.6	23	13.7	.004
Neurologic	6	7.1	6	3.6	.21
Psychiatric	7	8.3	25	14.9	.14
Other Cancer	19	22.6	24	14.3	.10

Abbreviations: CMC = comorbid medical conditions; ECOG PS = Eastern Cooperative Oncology Group performance status.
P values reported are χ^2 *P* values unless otherwise noted.
* P-values reported are ANOVA *P* values.
Comorbid conditions are defined as follows: pulmonary (asthma, chronic obstructive pulmonary disease), cardiac (congestive heart failure, coronary artery disease), vascular (pulmonary embolism), renal (chronic kidney disease), endocrine (diabetes mellitus, hypothyroidism, hyperthyroidism), neurologic (neuropathy, cerebrovascular accident), psychiatric (depression, bipolar disorder), and other cancer.
[a] Oxaliplatin monotherapy.
[b] All FOLFOX-based chemotherapy regimens, including FOLFOX, FOLFOX + bevacizumab.
[c] All CAPOX-based chemotherapy regimens, including CAPOX + bevacizumab.

Intolerance and Toxicity

Rates of chemotherapy administration did not differ between cases and controls by stage. There is no statistically significant difference in overall grade ≥ 3 treatment-related toxicity experienced by adults ≥ 75 years and their younger counterparts (56% cases vs. 65% controls; $P = .14$) (Table 2). Further evaluation by individual toxicity reveals a statistically significant increase in grade ≥ 3 fatigue in patients ≥ 75 years of age (38% cases vs. 12% controls; $P < .001$). Older patients did appear to have less grade ≥ 3 hematologic toxicity and neuropathy, which is not explained by rates of chemotherapy

Table 2 Frequency of Oxaliplatin-Based Chemotherapy Intolerance and Grade ≥ 3 Toxicity

Characteristic	Cases (n = 84)		Controls (n = 168)		*P* Value
	No.	%	No.	%	
Intolerance					
Dose Reduction	45	53.6	82	48.8	.48
Dose Delay	40	47.6	95	56.5	.18
Hospital/Facility Admission	36	42.9	49	29.2	.03
Toxicity					
Hematologic	16	19.0	59	35.1	.01
Neurologic	10	11.9	43	25.6	.01
Gastrointestinal	21	25.0	32	19.0	.27
Dermatologic	1	1.2	1	0.6	.62
Fatigue	32	38.1	20	11.9	< .001
Other	10	11.9	18	10.7	.78
Any Grade ≥ 3 Toxicity	60	71.4	115	68.5	.63

Table 3 Reason for Discontinuation of Oxaliplatin

Reason	Cases (n = 84)		Controls (n = 168)		*P* Value
	No.	%	No.	%	
Progression	46	54.8	60	35.7	.004
Completion	14	16.7	38	22.6	.27
Toxicity	14	16.7	40	23.8	.19
Loss to Follow-up	10	11.9	3	1.8	< .001
Patient Preference	0	0.0	9	5.4	.03

administration between cases and controls. There are no statistically significant differences in rates of intolerance for older compared with younger patients as measured by number of dose reductions (54% cases vs. 49% controls; $P = .476$) and number of dose delays (48% cases vs. 56% controls; $P = .18$). However older patients experienced statistically significant higher rates of hospital/facility admissions (43% cases vs. 29% controls; $P = .03$). The majority of older patients were hospitalized for complications of their disease (progression, failure to thrive, or pain) (71%); 6 patients were hospitalized for grade ≥ 3 treatment-related toxicity, and 4 patients were hospitalized for palliative or diagnostic procedures. In contrast, 65% of controls were hospitalized for complications of their disease (progression, failure to thrive, or pain), 19% were hospitalized for grade ≥ 3 treatment-related toxicity, and 7.4% were hospitalized for palliative or diagnostic procedures. Rates of discontinuation of Oxaliplatin due to grade ≥3 treatment-related toxicity appeared similar between cases and controls ($P = 0.19$) (Table 3). Odds of intolerance and grade ≥ 3 toxicity from oxaliplatin-based chemotherapy were not increased by any CMC (Table 4) or by the number of medications patients received (Table 5). There were no significant interactions of age (cases vs. controls) and number of CMCs (0, 1-2, ≥ 3) for dose reduction or delay ($P = .40$), hospital/facility admission ($P = .29$), and grade ≥ 3 toxicity ($P = .85$).

For added clinical significance, we examined the impact of age on combined endpoints of any grade ≥ 3 toxicity or hospital/facility admission. Although overall rates of toxicity or admission occurred for more than two thirds of the cohort, the rate of toxicity or admission did not differ significantly between cases and controls (77.4% vs. 76.8%; $P = .92$). These results did not differ appreciably when comparing those aged < 80 (77.5%) years to those aged ≥ 80 (71.4%) years ($P = .53$) or those aged 75 to 79 (79.4%) years to those aged ≥ 80 (71.4%) years ($P = .45$).

Exploratory Analysis of Chemotherapy Effectiveness

Analyses of overall survival are exploratory. Survival was calculated as the time from date of oxaliplatin initiation to date of death. For patients for whom the initial oxaliplatin start date was unknown (because of their initiating care elsewhere), survival from date of the initial oncologic visit was calculated. Patients who were still alive at the date of last contact were censored at this date. Overall survival at 1, 2, and 3 years was similar between adults ≥ 75 years and younger patients at a median follow-up of 52 months (overall survival, 1 year = 68% cases, 79% controls; 2 years = 43% cases, 57% controls; 3 years = 36% cases, 43% controls; $P = .25$) (Figure 1). As expected, overall survival is greater for patients with stage III vs. metastatic disease (Figure 2).

Table 4 Odds of Intolerance to Oxaliplatin-Based Chemotherapy by Comorbid Medical Conditions and Number of Medications[a]

Characteristic	Dose Delay OR (95% CI)	Dose Reduction OR (95% CI)	Hospital/Facility Admission OR (95% CI)
No. of Concurrent Medications	1.00 (1.00-1.00)	0.10 (1.00-1.00)	1.00 (1.00-1.00)
Comorbid Condition			
Pulmonary	1.65 (0.49-5.53)	1.15 (0.32-4.11)	0.59 (0.17-2.10)
Cardiac	0.68 (0.36-1.26)	1.20 (0.63-2.29)	0.92 (0.45-1.85)
Vascular	1.22 (0.42-3.58)	2.64 (0.67-10.36)	9.45 (1.15-77.96)
Renal[b]	0.17 (0.02-1.60)	—	2.73 (0.23-33.00)
Endocrine	1.39 (0.66-2.94)	0.85 (0.38-1.88)	1.49 (0.66-3.35)
Neurologic	0.53 (0.13-2.04)	3.39 (0.64-17.93)	2.96 (0.72-12.08)
Psychiatric	0.92 (0.35-2.45)	0.93 (0.37-2.36)	1.26 (0.40-4.00)
Any comorbidity	0.93 (0.70-1.23)	1.15 (0.83-1.59)	1.33 (0.96-1.83)

Abbreviations: CI = confidence interval; OR = odds ratio.
Odds ratio (> 1 implies positive association, < 1 implies negative association).
Conditional logistic regression (conditioned on matched set) was performed for occurrence of dose delay (yes/no), occurrence of dose reduction (yes/no), and hospital or facility admission (yes/no).
[a] Medications that are adjuncts to chemotherapy, eg, antiemetic agents, antidiarrheal agents, and stool softeners, are excluded.
[b] All patients with renal comorbidities had at least 1 dose reduction.

Table 5 Odds of Grade ≥ 3 Toxicity With Oxaliplatin-Based Chemotherapy by Comorbid Medical Condition

CMC	Hematologic Toxicity OR (95% CI)	Neurologic Toxicity OR (95% CI)	Gastrointestinal Toxicity OR (95% CI)	Fatigue Toxicity OR (95% CI)	Any Toxicity OR (95% CI)
Pulmonary	1.88 (0.39-8.92)	0.19 (0.02-1.72)	0.33 (0.06-1.80)	1.18 (0.30-4.63)	0.67 (0.19-2.32)
Cardiac	0.35 (0.15-0.78)	0.74 (0.36-1.50)	0.75 (0.33-1.70)	1.57 (0.73-3.35)	0.76 (0.38-1.50)
Vascular	1.50 (0.43-5.23)	0.35 (0.07-1.73)	2.12 (0.47-9.48)	3.58 (0.91-14.11)	2.10 (0.52-8.43)
Renal[a]	—	—	—	0.59 (0.05-7.43)	0.17 (0.02-1.60)
Endocrine	0.87 (0.36-2.12)	0.75 (0.30-1.89)	2.63 (1.02-6.82)	1.96 (0.81-4.76)	0.95 (0.43-2.08)
Neurologic	1.00 (0.18-5.46)	0.80 (0.16-4.12)	1.23 (0.26-5.75)	3.36 (0.83-13.55)	2.43 (0.60-9.78)
Psychiatric	1.82 (0.62-5.40)	1.11 (0.37-3.34)	0.50 (0.13-1.93)	0.28 (0.08-1.00)	0.79 (0.30-2.07)
Other Cancer	0.84 (0.30-2.32)	1.06 (0.46-2.47)	2.22 (0.69-7.10)	1.81 (0.76-4.32)	0.74 (0.32-1.71)

Abbreviations: CI = confidence interval; CMC = comorbid medical condition; OR = odds ratio.
[a] All patients with renal comorbidities had neurologic toxicities and only 1 each had any hematologic or gastrointestinal toxicities, so valid logistic regressions could not be performed for these toxicities.

However, overall survival appeared similar for cases and controls regardless of stage of disease (Figure 2).

Discussion

We evaluated the toxicity and intolerance of oxaliplatin-based chemotherapy regimens in adults ≥ 75 years of age with stage III and metastatic CRC compared with a matched younger cohort receiving treatment at 2 academic hospitals in Boston, MA. The study shows that older age does not have a statistically significant impact on rates of intolerance or toxicity with oxaliplatin-based chemotherapy. Although analysis of individual toxicities reveals an increased rate of grade ≥ 3 treatment-related fatigue experienced by adults ≥ 75 years, the overall grade ≥ 3 treatment-related toxicity does not differ significantly between cases and controls. Older patients were observed to have higher rates of hospitalization compared with younger patients; however the majority of hospitalizations in both groups were due to complications of their disease.

We also sought to determine if there is a difference in the number of comorbid medical conditions for older compared with younger adults and whether that impacts rates of intolerance or toxicity. The study shows that older adults have a greater mean total number of comorbid conditions and take more medications than do their younger counterparts. However the absolute number of each comorbid condition is similar between cases and controls, with the exception of a significantly greater number of cases having cardiac comorbid conditions ($P < .001$). This finding is likely explained by the high prevalence of cardiac disease in the general population and the increased risk with older age.[9] Further, the presence of an increased mean number of comorbid conditions does not have a statistically significant impact on rates of intolerance or toxicity in this cohort. In exploratory analysis, overall survival is similar between cases and controls at a median follow-up of 52 months.

Figure 1 Kaplan-Meier Curve: Overall Survival From Date of Oxaliplatin Initiation (DOO) or Date of Initial Oncologic Visit (DOV) to Time of Death in Cases vs. Controls

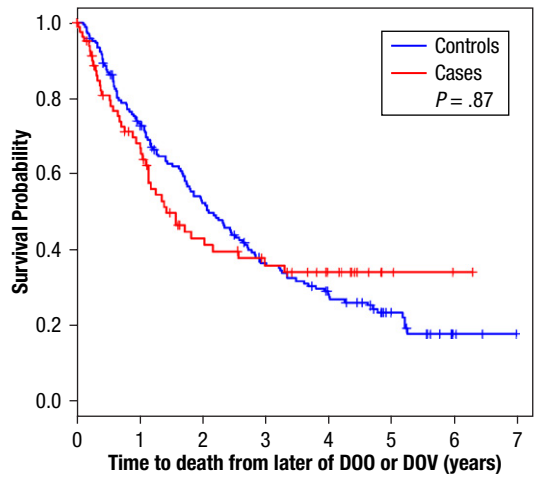
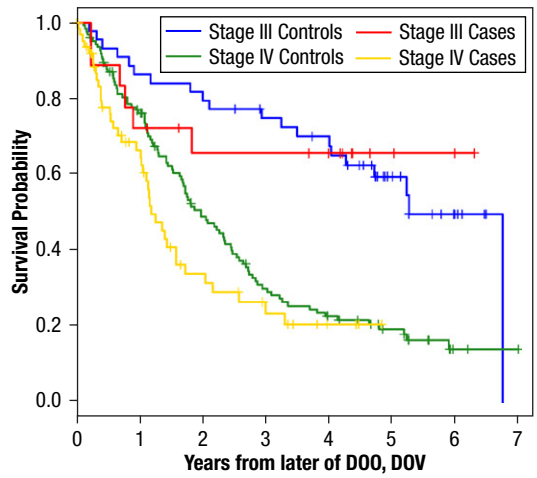


Figure 2 Kaplan-Meier Curve: Overall Survival by Stage From The Later Occurrence of Date of Oxaliplatin Initiation (DOO) or Date of Initial Oncologic Visit (DOV) in Cases vs. Controls



P Values:
Overall: $P < .001$
Stage III cases vs. controls: $P = .986$
Stage IV cases vs. controls: $P = .097$

Overall, this study shows similar rates of tolerance and toxicity patterns for older adults ≥ 75 years of age with stage III and metastatic CRC and their younger counterparts, with no significant difference in overall survival in exploratory analysis between the 2 age groups. The finding of significantly increased grade ≥ 3 fatigue in elderly patients receiving oxaliplatin-based chemotherapy has been previously demonstrated by Goldberg et al and warrants further exploration.[11]

One pooled analysis and 3 subset analyses of oxaliplatin-based chemotherapy failed to demonstrate a survival benefit in the adjuvant setting for older adults.[3,8,9] Although updated survival outcomes from the MOSAIC study showed a superior 5-year disease-free survival and 6-year overall survival for patients with stage III disease, subset analysis of the older cohort showed that observed disease-free survival benefit at 3 years in patients ≥ 65 years of age was not maintained after 6 years of follow-up.[13,14] Similarly older adults receiving bolus 5-FU in combination with oxaliplatin (FLOX) did not derive a disease-free survival benefit at 7 years compared with younger patients.[13] Pooled analysis of the Adjuvant Colon Cancer Endpoints (ACCENT) database, incorporating the MOSAIC and NSABP C-07 trials, demonstrated no disease-free or overall survival benefit of oxaliplatin-based chemotherapy compared with 5-FU/LV in patients aged ≥ 70 years.[15] Subsequent evaluation of oxaliplatin in this population is based on a phase III trial comparing capecitabine and oxaliplatin to bolus 5-FU/LV in 1886 patients with stage III colon cancer (n = 409 ≥ 70 years). These data did not support a survival benefit among older adults, although the study was underpowered in this age group.[16] The hazard ratio for 5-year overall survival was 0.94 (95% confidence interval [CI], 0.66-1.34) for ≥ 70 years of age; for 3-year disease-free survival, the hazard ratio was 0.87 (95% CI, 0.63-1.18) for ≥ 70 years of age in comparison with younger patients. Furthermore, older adults experienced more grade ≥ 3 or toxicity with lower dose intensity.

Analysis regarding the mechanism of this observed lack of survival benefit in the adjuvant setting is forthcoming from MOSAIC[9] and NSABP C-07[8] investigators. Thus far, lack of overall survival benefit is not explained by differences in dose intensity, tumor characteristics, or CMCs of elderly patients based on MOSAIC data presented at the 2010 Gastrointestinal Cancers Symposium of the American Society of Clinical Oncologists.[9] Further analysis is needed regarding the impact of dose intensity, number and severity of CMCs, and toxicity on survival outcomes for older adults receiving oxaliplatin in the adjuvant setting in clinical trials.[14] In an analysis of 6465 patients aged ≥ 75 years from 4 population-based cohorts in the adjuvant setting, Sanoff et al noted declining use of adjuvant chemotherapy and oxaliplatin with increasing age.[17] However, 3-year overall survival was higher among those who did receive adjuvant chemotherapy, specifically those receiving oxaliplatin in the SEER/Medicare cohorts but not in other cohorts.

In the metastatic setting, survival benefit is confounded by deaths from competing medical conditions in the older population. Consequently, tolerance and toxicity are more significant metrics of treatment outcome. The present study confirms previous examination of an effectiveness cohort in the metastatic setting for oxaliplatin-based chemotherapy and demonstrates no statistically significant difference in treatment tolerance, toxicity, or survival in exploratory analyses for older adults (≥ 75 years) compared with a matched younger cohort (< 75 years). In a medical record review of treatment patterns for metastatic CRC in community oncology practices, McKibbin et al noted that patients ≥ 65 years were less likely to receive combination

therapy with oxaliplatin than were their younger counterparts.[18] Yet, those patients who receive oxaliplatin-based therapy appear to derive a survival benefit similar to that of younger patients. In a pooled analysis of 614 patients enrolled in 3 advanced CRC trials and 1 in the adjuvant setting (MOSAIC), Goldberg et al noted a similar efficacy and toxicity profile for patients regardless of age.[11] Although older adults appeared to receive a similar survival benefit as historical controls, 67% of patients experienced grade ≥ 3 toxicity,[11] reflecting a significant degree of intolerance to oxaliplatin within a highly selected clinical trial population.

Despite the fact that the prevalence of CRC is higher in older adults, previous studies rarely had sufficient representation of adults ≥ 75 years of age to provide adequate data to draw conclusions regarding tolerance and toxicity of oxaliplatin-based chemotherapy regimens. The cohort of patients enrolled in our study has the unique strength of providing information on the older population, which tends to be underrepresented in clinical trials. In this cohort, 25% of the patients enrolled were ≥ 80 years in comparison with a pooled analysis of 3 metastatic and 1 adjuvant oxaliplatin-based chemotherapy trials in which only 4% of the analysis cohort was ≥ 75 years, with < 1% of the cohort ≥ 80 years.[11]

Limitations of our study are those inherent to retrospective case-control studies relying on medical record review. We are unable to confirm the completeness of the comorbid medical condition extrapolation or comment on severity. However, both hospitals use an electronic medical record with actively maintained problem lists. Although toxicities recorded occurred during the active treatment period, we did not include specific dates of occurrence relative to initiation of oxaliplatin, limiting the validity of survival analysis. For that reason, survival analysis is exploratory for the sake of generating hypotheses regarding observed survival differences in the literature for older and younger adults. We cannot detail the cause of death for patients enrolled; thus any survival mentioned may include non–cancer-related death from competing medical conditions. Finally, although the population studied did not participate in randomized clinical trials, there remains a potential selection bias given that patients able to receive treatment at an National Cancer Institute center may differ from those managed in community settings.

The present analysis provides important information regarding safety and comparative effectiveness of oxaliplatin-based chemotherapy in older adults with stage III and metastatic CRC not enrolled in clinical trials. Further investigation is needed to adequately prospectively assess the degree to which survival outcomes are impacted by toxicity and intolerance in older adults with metastatic CRC. Additionally, data detailing competing causes of death among older adults with CRC may clarify the incremental benefit of combination chemotherapy regimens.

We have shown that age itself is not predictive of tolerance or toxicity to oxaliplatin-based chemotherapy regimens, even when considering that older adults in this study had a greater mean number of CMCs compared with younger patients. Hence there is a need for accurate assessment tools to guide clinical decision making for older adults. The cancer-specific geriatric assessment tool was developed by Hurria et al[19], and subsequently validated.[14,20] It has been shown to predict treatment outcomes better than the ECOG PS or physician judgment alone[14,19,21-23] as well as toxicity with chemotherapy regimens,[14] providing useful clinical adjunctive information beyond age, CMCs, or medications alone. Further validation in advanced CRC is ongoing in a cooperative group study.

Based on the present literature, older adults appear to experience similar safety and effectiveness from oxaliplatin-based chemotherapy in the nonclinical trial setting for both stage III and metastatic CRC. This result is similar to previous analyses in the metastatic setting,[11] and some[3,24] but not all studies in the adjuvant setting. Further study in larger cohorts is warranted to determine if the observed effect is attenuated by the presence or severity of CMCs within this growing subset of patients. Until the findings in this regional study are confirmed, we suggest oncologists consider extending standard chemotherapy treatment to all patients, regardless of age, for stage III and metastatic CRC. Further, incorporation of geriatric assessment strategies may increase patient receipt of standard and tolerable treatment regardless of age.

Clinical Practice Points

- While safety and efficacy of oxaliplatin-based chemotherapy regimens for colorectal cancer (CRC) has been demonstrated in adults ≥ 75 years enrolled in clinical trials, safety and effectiveness outside the trial setting are less established.
- We retrospectively collected cases of patients ≥ 75 years old diagnosed with stage III and metastatic CRC initiating treatment between January 2000 – January 2007 at two academic hospitals in Boston, MA.
- There was no significant difference in grade ≥ 3 treatment-associated toxicities between the cases and controls (71.4% vs. 68.5%, $P = .63$). Further there was no statistically significant difference between cases and controls for combined endpoints of any grade ≥ 3 toxicity or hospital/facility admission ($P = .92$). With a median follow-up of 52 months, 2-year overall survival was similar between cases and controls (43% vs. 52%, $P = .87$).
- Older adults with stage III and metastatic colorectal cancer treated outside of a clinical trial experienced comparable safety and effectiveness of oxaliplatin-based chemotherapy regimens compared to younger adults. Further study is warranted to determine if this effect is attenuated by the presence or severity of comorbid medical conditions within this growing subset of patients.

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Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Schrag D, Cramer LD, Bach PB, et al. Age and adjuvant chemotherapy use after surgery for stage III colon cancer. *J Natl Cancer Inst* 2001; 93:850-7.
2. Sugrue MM, KM, Hainsworth J, et al. Safety and effectiveness of bevacizumab plus chemotherapy in elderly patients with mCRC: results from the BRiTE registry. Presented at 2007 Gastrointestinal Cancers Symposium, January 19-21, 2007; Orlando, FL. Abstract 345. Available at: www.asco.org. Accessed October 1, 2012.
3. Haller DG, Tabernero J, Maroun J, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011; 29:1465-71.

4. Hutchins LF, Unger JM, Crowley JJ, et al. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999; 341:2061-7.
5. Stewart JH, Bertoni AG, Staten JL, et al. Participation in surgical oncology clinical trials: gender-, race/ethnicity-, and age-based disparities. *Ann Surg Oncol* 2007; 14:3328-34.
6. Townsley CA, Selby R, Siu LL. Systematic review of barriers to the recruitment of older patients with cancer onto clinical trials. *J Clin Oncol* 2005; 23:3112-24.
7. Yazdanyar A, Newman AB. The burden of cardiovascular disease in the elderly: morbidity, mortality, and costs. *Clin Geriatr Med* 2009; 25:563-77, vii.
8. Yothers G, O'Connell MJ, Allegra CJ, et al. Oxaliplatin as adjuvant therapy for colon cancer: updated results of NSABP C-07 trial, including survival and subset analyses. *J Clin Oncol* 2011; 29:3768-74.
9. Tournigand A, Bachet, Teixeira, et al., for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) investigators and GERCOR. FOLFOX4 as adjuvant therapy in elderly patients with colon cancer: subgroup analysis of the MOSAIC trial. *J Clin Oncol* 2010; 28(suppl):abstract 3522. Available at: www.asco.org. Accessed October 1, 2012.
10. Ford JG, Howerton MW, Lai GY, et al. Barriers to recruiting underrepresented populations to cancer clinical trials: a systematic review. *Cancer* 2008; 112:228-42.
11. Goldberg RM, Tabah-Fisch I, Bleiberg H, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 2006; 24:4085-91.
12. Surveillance Epidemiology and End Results. (SEER). Available at: http://seer.cancer.gov/. Accessed: October 1, 2012.
13. Yothers G, O'Connelll L, Colangelo JP, et al. 5-FU and leucovorin with or without oxaliplatin for adjuvant treatment of stage II and III colon cancer: long-term follow-up of NSABP C-07 with survival analysis. 2010 Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, FL. Available at: www.asco.org. Accessed: October 1, 2012.
14. Hurria A, TK, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011; 29:3457-64.
15. Jackson McCleary NA, Meyerhardt J, Green E, et al. Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: findings from the ACCENT database. *J Clin Oncol* 2009; 27(suppl):abstract 4010.
16. Haller DG, Cassidy J, Tabernero J, et al. Efficacy findings from a randomized phase III trial of capecitabine plus oxaliplatin versus bolus 5-FU/LV in stage III colon cancer (NO16968): no impact of age on disease-free survival (DFS). 2010 Gastrointestinal Cancers Symposium; January 22-24, 2010; Orlando, FL. Abstract 284. Available at: www.asco.org. Accessed: October 1, 2012.
17. Sanoff HK, Carpenter WR, Stümer, et al. The effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012; 30:2624-34.
18. McKibbin T, Frei CR, Greene RE, et al. Disparities in the use of chemotherapy and monoclonal antibody therapy for elderly advanced colorectal cancer patients in the community oncology setting. *Oncologist* 2008; 13:876-85.
19. Hurria A, Gupta S, Zauderer M, et al. Developing a cancer-specific geriatric assessment: a feasibility study. *Cancer* 2005; 104:1998-2005.
20. Hurria A, Cirrincione CT, Muss HB, et al. Implementing a geriatric assessment in cooperative group clinical cancer trials: CALGB 360401. *J Clin Oncol* 2011; 29: 1290-6.
21. Wedding U, Ködding D, Pientka L, et al. Physicians' judgement and comprehensive geriatric assessment (CGA) select different patients as fit for chemotherapy. *Crit Rev Oncol Hematol* 2007; 64:1-9.
22. Extermann M, Hurria A. Comprehensive geriatric assessment for older patients with cancer. *J Clin Oncol* 2007; 25:1824-31.
23. Hurria A, Lichtman SM, Gardes J, et al. Identifying vulnerable older adults with cancer: integrating geriatric assessment into oncology practice. *J Am Geriatr Soc* 2007; 55:1604-8.
24. Sanoff HK, Carpenter WR, Stürmer T, et al. Effect of adjuvant chemotherapy on survival of patients with stage III colon cancer diagnosed after age 75 years. *J Clin Oncol* 2012; 30:2624-34.