

Chronological Age and Risk of Chemotherapy Nonfeasibility:

A Real-Life Cohort Study of 153 Stage II or III Colorectal Cancer Patients Given Adjuvant-modified FOLFOX6

Marie Laurent, MD,*† Gaétan Des Guetz, MD,‡
 Sylvie Bastuji-Garin, MD, PhD,*§|| Stéphane Culine, MD, PhD,¶##
 Philippe Caillet, MD,*† Thomas Aparicio, MD, PhD,‡**
 Etienne Audureau, MD, PhD,*§ Muriel Carvahlo-Verlinde, PharmD,††
 Nicoleta Reinald, MD,*† Christophe Tournigand, MD, PhD,‡‡§§
 Thierry Landre, PharmD,|| Aurélie LeThuat, MSc,*§||
 Elena Paillaud, MD, PhD,*† and Florence Canoui-Poitaine, MD, PhD*§

Objectives: To assess nonfeasibility of adjuvant-modified FOLFOX6 chemotherapy in patients with stage II or III colorectal cancer.

Methods: Consecutive patients managed between 2009 and 2013 in 2 teaching hospitals in the Paris urban area were included in the CORSAGE (COlorectal canceR, AGE, and chemotherapy fEasability study) cohort study. Nonfeasibility was defined by the frequencies of empirical first-cycle dose reduction (>15%), early discontinuation (<12 cycles), and low relative dose intensity (RDI) (<0.85). Risk factors for chemotherapy nonfeasibility were identified using multivariate logistic regression.

Results: Among 153 patients, 56.2% were male (median age, 65.6 y; 35.3% ≥ 70 y; 7.3% with performance status [PS] ≥ 2). For 5-fluorouracil (5-FU), 20.9% of patients had first-cycle dose reduction and 28.1% early discontinuation; RDI was 0.91 (25th to 75th percentiles, 0.68 to 0.99). Factors independently associated with first-cycle 5-FU dose reduction were aged 65 to 69 years versus those younger than 65 years (adjusted odds ratio [aOR], 5.5; 95% confidence interval [CI], 1.5-19.9) but not age 70 years and older, PS ≥ 2 (aOR, 6.02; 95% CI, 1.15-31.4), higher Charlson Comorbidity Index (aOR_{1-point increase}, 1.4; 95% CI, 1.05-1.82), or larger number of medications (aOR 1-medication increase, 1.19; 95% CI, 1.00-1.42). Oxaliplatin dose reduction occurred in 52.3% of patients and early discontinuation in 62.7%; the latter was more common in the 70 years and older group (92.6% vs. 74.6% in the <65-y group; $P = 0.01$); RDI was 0.7 (95% CI, 0.55-0.88).

Conclusions: In the real-world setting, compared with their younger and older counterparts, patients aged 65 to 69 years given modified FOLFOX6 for stage II or III colorectal cancer had higher frequencies of 5-FU nonfeasibility defined based on first-cycle dose reduction, early discontinuation, and RDI; and these differences were independent from PS, comorbidities, and number of medications.

Key Words: colorectal cancer, feasibility, relative dose intensity, age, FOLFOX6, adjuvant, medication, early discontinuation

(*Am J Clin Oncol* 2015;00:000–000)

Colorectal cancer (CRC) is the third most common cancer in men, the second in women, and the fourth most common cause of death from cancer.¹ The incidence of CRC increases with age: among patients with newly diagnosed CRC in France in 2008, 71.3% were 65 years or older and 42.3% 75 years or older. The treatment of CRC is multimodal (surgery and/or chemotherapy and/or radiotherapy and/or targeted therapy) and depends on the tumor site and stage. Since the early 1990s, numerous clinical trials and meta-analyses have established the efficacy of adjuvant chemotherapy, particularly with fluoropyrimidines such as 5-fluorouracil (5-FU), in patients with CRC. Data reported in 2004 demonstrated that adding oxaliplatin was superior over fluoropyrimidine alone.^{2,3} The FOLFOX combination of oxaliplatin, infusional and bolus 5-FU, and leucovorin for 6 months is now considered one of the main adjuvant treatments for patients with stage III CRC or high-risk stage II CRC, although recent data challenge the usefulness of adding oxaliplatin in patients aged 70 to 75 years.^{4,5}

Several observational studies suggest that less aggressive treatment in terms of both chemotherapy initiation and drug selection may be more common in older CRC patients than in their younger counterparts.^{6–8} Older age may constitute a barrier to optimal treatment, due in part to comorbidities, fear of toxicities, lack of clinical trial data from older patients, social marginalization, or preferences of patients and physicians.^{7,9} Whether the nonfeasibility of chemotherapy increases with advancing age is unclear,^{9–12} and few studies have specifically addressed this issue. The definition and assessment methods of chemotherapy nonfeasibility are not universally

From the *IMRB-EA 7376 CEpiA Clinical Epidemiology And Ageing, Faculty of Medicine, A-TVB DHU; §§Faculty of Medicine, Paris-Est University; †Geriatric Oncology Unit, Geriatrics Department; §Public Health Department, APHP, Henri Mondor Hospital; ||Research Clinic Unit; ††Pharmacy Department; ‡‡Medical Oncology Department, APHP, Henri Mondor Hospital, Creteil; ‡Gastro Enterology and Digestive Oncology, APHP, Avicennes Hospital; || Geriatric Oncology Unit, Pharmacy Department, APHP, Rene Muret Hospital, Bobigny; ¶Medical Oncology Department, APHP, Saint-Louis Hospital; #Faculty of Medicine, Paris Diderot University; and **Sorbonne Paris Cité-Paris 13 University, Paris, France.

E.P. and F.C.-P. contributed equally.

The authors declare no conflicts of interest.

Reprints: Marie Laurent, MD, Service de Médecine interne et gériatrie, Hôpital Albert Chenevier, 40 rue de Mesly, Créteil 94000, France.

E-mail: marie.laurent@aphp.fr.

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ISSN: 0277-3732/15/000-000

DOI: 10.1097/COC.0000000000000233

agreed on. Previous studies have used dosage,^{9,10} relative dose intensity (RDI) (received dose divided by the planned dose),^{13,14} number of cycles, spacing of cycles,⁹ or a combined endpoint¹² including mortality and/or grade III or IV toxicity^{10,12} and/or treatment interruption and/or admission during chemotherapy.¹⁰ Large studies in patients with breast cancer or non-Hodgkin lymphoma¹⁵ used RDI measures and demonstrated that a low RDI was strongly associated with adverse patient outcomes.^{13,16,17} In CRC, few data are available, and most come from small clinical series focused on patients with metastases and from clinical trials. A recent study assessed RDIs in 36 and 30 patients included in phase II trials of FOLFIRI and FOLFOX6 and found that low RDI was associated with adverse clinical outcomes.¹⁸ In another study, older age was associated with lower 5-FU RDI values, but no multivariate analysis was performed.¹⁹ Therefore, we designed a survey of patients given adjuvant chemotherapy for CRC in the real-life setting, with a multivariate analysis.

Our objectives were, first, to assess chemotherapy nonfeasibility based on first-cycle dose reduction, early discontinuation, and low RDI values; and second, to identify factors associated with chemotherapy nonfeasibility, with special attention to chronological age.

METHODS

The study complied with the Declaration of Helsinki. The study protocol was approved by the Ile-de-France IX institutional review board of the Henri-Mondor Teaching Hospital, Creteil, France. This report complies with the Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement.²⁰

Patients and Design

The CORSAGE (COlorectal canceRS, AGe and chemotherapy fEasability study) cohort study was conducted in 2 teaching hospitals (584 and 906 beds, respectively) in Bobigny and Creteil, Paris conurbation, France. Consecutive patients aged 18 years or over who started receiving the modified FOLFOX6 regimen for CRC stage II or III between January 1, 2009, and February 26, 2013, were included. Modified FOLFOX6 consisted of leucovorin 400 mg/m²/d and oxaliplatin 85 mg/m² as a 2-hour infusion on day 1 followed by bolus 5-FU, 400 mg/m² then by a 46-h 5-FU infusion of 2400 mg/m².²¹ This cycle was repeated every 2 weeks for a total of 12 cycles. Patients who received part of the FOLFOX6 cycles in another hospital were not included.

Baseline Characteristics

The date of study inclusion was the date of the first modified FOLFOX6 cycle. The following sociodemographic and baseline patient characteristics were extracted from the hospital electronic medical charts (MediWeb version 4.0-Copyright 1997-2008 DIH-APHP, Paris, France): center, age, sex, location of cancer (colon or rectum) and stage (low-risk II, high-risk II, or III), body mass index (BMI [kg/m²]), performance status (PS: 0, 1, or ≥ 2), Charlson Comorbidity Index (CCI), and number of prescription medications for comorbidities irrespective of therapeutic class. Malnutrition was defined as BMI < 21 kg/m² in patients aged 70 years or over and as BMI < 18.5 kg/m² in younger patients.

Chemotherapy Nonfeasibility

Data on chemotherapy were recorded prospectively in the hospital chemotherapy database (CHIMIO version 2.0). The 5-FU and oxaliplatin doses given at each cycle and the reasons

for any dose modifications, including toxicities, were collected from the chemotherapy database and hospital electronic medical charts. In the oncology departments, the dates and doses of 5-FU and oxaliplatin given during each cycle were recorded routinely in real time and validated by the pharmacist in charge. Toxicities were classified using Common Terminology Criteria for Adverse Events (CTCAE version 4.03).

We assessed 3 measures of chemotherapy nonfeasibility, separately for 5-FU and oxaliplatin: first-cycle dose reduction defined as an administered dose at least 15% lower than the planned dose²²; early discontinuation, defined as <12 cycles, since French and international guidelines²³ define the full modified FOLFOX6 regimen as 12 cycles; and RDI < 0.85.^{18,22,24,25} RDI was computed as the received dose over the planned dose; for 5-FU both the bolus and the infusions were counted.

Survival

Overall survival (OS) after 1 year was determined by chart review. OS was defined as the time from treatment initiation to death, last follow-up within the first year, or end of the first year of follow-up, whichever occurred first.

Statistical Analysis

Baseline patient characteristics and chemotherapy parameters were described using number (%) for qualitative data and mean (SD) or median (interquartile range), as appropriate, for quantitative data.

No age cutoff for defining elderly patients has been universally agreed on, but usual cutoffs in the international literature are between 65 and 70 years. Therefore, we compared 3 age groups (<65 y, 65 to ≤ 70 y, and >70 y), globally and with pairwise comparisons after Bonferroni correction.

We conducted univariate and multivariate analyses to identify factors associated with first-cycle dose reduction (>15%), early discontinuation (<12 cycles), and reduced RDI (<0.85), separately for 5-FU and oxaliplatin. Variables were considered in continuous after verifying linearity; for nonlinear variables, we tested several categorizations, using >2 categories to limit loss of power and residual confounding.²⁶ We found that age was not linear; for the univariate and multivariate analyses, we used a 3-category model (<65; 65 to 70; and ≥ 70 y), which provided a better fit than did 2-category models.

Univariate analyses relied on the χ^2 test or Fisher exact test for qualitative variables and the *t* test or nonparametric Wilcoxon Mann-Whitney test for quantitative variables. Variables yielding *P* < 0.15 by univariate analysis were entered into multivariate logistic regression models. To avoid introducing highly correlated variables, we assessed correlations using the Cramer's *V* for categorical variables and the nonparametric Spearman rank correlation (ρ) for quantitative variables; a threshold of 0.50 was selected to define strong correlations. Adjusted odds ratios (aORs) with their 95% confidence intervals (95% CIs) were estimated. We conducted sensitivity analyses by defining dose reduction as an at least 10%, 20%, or 30% dose decrease.

Associations linking early 5-FU or oxaliplatin discontinuation and overall 1-year survival were assessed using Kaplan-Meier survival curves and the log-rank test. The hazard ratios (HRs) and their 95% CIs were computed to estimate relative risks. Early discontinuation was handled as a time-dependent variable. The Cox proportional hazards model was used for multivariate analysis.

We did not perform multiple imputations for missing data. All tests were 2-tailed. Values of $P < 0.05$ were considered statistically significant. The data were analyzed using STATA statistical software version 11.0 (College Station, TX).

RESULTS

Baseline Characteristics

We included 153 consecutive patients with CRC who started adjuvant-modified FOLFOX6 chemotherapy between January 2009 and February 2013. Median age was 65.6 years (56.3 to 72 y), 56.2% of patients were male, and 87.6% had colon cancer; 111 patients (72.5%) were stage III, 40 (26.1%) stage II (including 22 with high-risk stage II), and 2 (1.3%) stage II or III. PS was 0 in 60.1% of patients, 1 in 32.6%, and ≥ 2 in 7.3%. Median CCI was 0.5 (0 to 2). Overall, 93 patients (67.4%) were receiving one or more medications for comorbidities; the median number of medications was 3 (2 to 6), 27 (29%) patients took 4 to 9 medications, and 3 (3.6%) patients took ≥ 10 medications.

Table 1 reports the comparison of the main characteristics across the 3 age groups.

Descriptive Analysis of Chemotherapy

5-FU

For 5-FU, first-cycle dose reduction occurred in 32 (20.9%) patients, alone in 29 patients, and combined with

oxaliplatin first-cycle dose reduction in 3 patients. Known reasons for dose reductions of first-cycle 5-FU only were declining functional status ($n = 7$) and physician concern about toxicities ($n = 19$); the reasons were unknown for 3 patients. Among patients with 5-FU first-cycle dose reduction, 16 (50%) had early discontinuation, at a median of 7 cycles (3 to 9). Among the 121 patients without first-cycle 5-FU dose reduction, 76 (62.8%) had 5-FU dose reduction between the 2nd and 12th cycles (median, 5th cycle [4 to 8]) and 27 (22.3%) had early discontinuation at a median of 9 cycles [5 to 10]. No patient had early discontinuation without previous dose reduction. The main reasons for early discontinuation or dose reduction of 5-FU between the 2nd and 12th cycles were hematological toxicity (38.7%), neurological toxicity (25.3%), other toxicities (10.7%), disease progression (4%), and patient refusal to continue chemotherapy (2.7%); the reason was unknown in 18.7% of patients. Median 5-FU RDI was 0.91 (0.68 to 0.99) with a median of 12 (11 to 12) cycles, indicating that 50% of the patients received 91% or more of the planned dose and 12 cycles. RDI was highest in patients younger than 65 years, lowest in those aged 65 to 69 years, and intermediate in those aged 70 years or over (Fig. 1).

Oxaliplatin

Oxaliplatin dose reduction occurred at the first cycle in only 4 (2.6%) patients (combined with 5-FU dose reduction in 3 patients) and between the 2nd and 12th cycles in 129 (84.3%)

TABLE 1. Patients and Chemotherapy Characteristics in the 3 Age Groups <65, 65 to 70, and ≥ 70 Years Old: The CORSAGE Cohort Study

	Age < 65	65-70	Age ≥ 70	Global Comparison	<65 Vs. 65-70	65-70 Vs. ≥ 70	<65 and ≥ 70
	n = 67	n = 32	n = 54	P*	P†	P†	P†
Age (median [Q1-Q3]) (y)	55.2 (48.6-60.3)	67 (66-68.3)	74.6 (72-76.1)				
Males	32 (47.7)	25 (78.1)	29 (53.7)	0.016	0.004	0.024	0.51
Colon cancer	51 (76.1)	31 (96.9)	52 (96.3)	0.001	0.01	0.888	0.002
PS (N = 138)							
PS = 0	48 (82.8)	16 (53.3)	19 (38)	<0.0001	0.003	0.055	<0.0001
PS = 1	8 (13.8)	14 (46.7)	23 (46)				
PS ≥ 2	2 (3.4)	0	8 (16)				
BMI (mean [SD]) (kg/m ²)	23.1 (4.7)	24.8 (5)	23.7 (3.1)	0.05	0.10	0.22	0.40
Malnutrition	10 (14.9)	4 (12.5)	10 (18.5)	0.74	0.74	0.46	0.60
Charlson Comorbidity Index (median [Q1-Q3])	0 (0-1)	1 (0-2)	1 (0-3)	0.001	0.003	0.055	<0.0001
No. medications (median [Q1-Q3])	0 (0-2)	3 (2-5)	3 (1-7)	0.0001	<0.0001	0.360	<0.0001
No. medications in patients receiving at least 1 medication (median [Q1-Q3]) (N = 93)	2 (1-4)	3 (2-5)	5 (2.5-7)	0.004	0.09	0.038	0.0010
5-FU							
Ordinal cycle number with dose reduction (median [Q1-Q3])	5 (4-7)	2 (1-6.5)	4 (1-6)	0.90	0.99	0.72	0.68
First-cycle dose reduction ($\geq 15\%$)	4 (6.0)	13 (40.6)	15 (27.8)	<0.0001	0.0001	0.219	0.001
Early discontinuation (<12 cycles)	11 (16.4)	14 (43.7)	18 (33.3)	0.010	0.003	0.33	0.030
Oxaliplatin							
Ordinal cycle number with dose reduction (median [Q1-Q3])	6 (1-8)	6 (3-8)	5 (3-8)	0.28	0.50	0.93	0.37
First-cycle dose reduction ($\geq 15\%$)	2 (3)	0	2 (3.7)	0.56			
Dose reduction from 2nd to 12th cycle	50 (74.6)	29 (90.6)	50 (92.6)	0.014	0.06	0.74	0.009
Early discontinuation (<12 cycles)	36 (53.7)	23 (71.9)	37 (68.5)	0.120	0.085	0.74	0.01

Malnutrition was defined as BMI <21 kg/m² in patients aged 70 years or over and as BMI <18.5 kg/m² in younger patients.

*Global test: Pearson χ^2 or Fisher test for qualitative variables; Kruskal-Wallis for quantitative variables are in n (%) otherwise indicated.

†Comparison between age groups: between <65 and 65-70 years, between 65-70 and ≥ 70 years, between <65 and ≥ 70 years: $P < 0.017$ were considered significant using Bonferroni correction.

BMI indicates body mass index; CORSAGE, COlorectal canceR, AGe and chemotherapy fEasability study; PS, performance status; Q1, quartile 1; Q3, quartile 3.

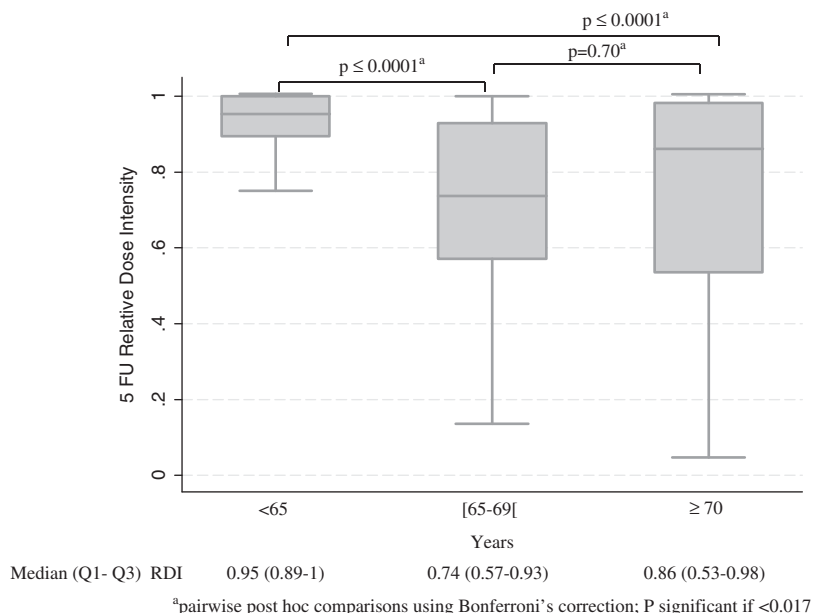


FIGURE 1. 5-fluorouracil relative dose intensity (RDI) across age groups.

patients, at a median of 6 [4 to 8] cycles. The reason for first-cycle oxaliplatin dose reduction was renal dysfunction in 2 of the 4 patients; the reason was unknown in the other 2 patients. Oxaliplatin dose reduction was followed by early discontinuation in 90 (69.8%) patients, after a median of 9 cycles [7 to 12] 6 patients had early discontinuation without previous dose reduction. The main reasons for early discontinuation were neurological toxicity (n=46, 51.1%), hematological toxicity (n=10, 11.1%), other toxicities (n=15, 16.6%), a decline in general health (n=6, 6.6%), disease progression (n=3, 3.3%), and unknown (n=16, 17.7%). Median oxaliplatin RDI was 0.7 [0.55 to 0.88] and median number of oxaliplatin cycles was 10 [7 to 12].

Factors Associated With Chemotherapy Nonfeasibility

5-FU

By univariate analysis, the subgroup with first-cycle 5-FU dose reduction had a higher proportion of patients with PS ≥ 2 (18.7% vs. 3.8%; $P=0.004$), higher CCI values (1.5 [1 to 3] vs. 0 [0 to 1.5]; $P=0.001$), and a larger number of medications (4 [3 to 6.5] vs. 1 [0 to 3]; $P<0.0001$) compared with patients with no dose reduction. The 65- to 69-year age group had higher proportions of patients with first-cycle dose reduction and early discontinuation, as well as a lower RDI value, compared with the groups of patients younger than 65 years and 70 years or older (Table 1).

Number of medications correlated strongly with CCI ($\rho=0.71$, $P<0.0001$) and was therefore not introduced into the multivariate model adjusted for CCI. By multivariate analysis, compared with the group aged younger than 65 years, the group aged 65 to 69 years had a higher proportion of patients with first-cycle 5-FU dose reduction, whereas the group aged 70 years and older did not (Table 2). Other factors independently associated with first-cycle 5-FU dose reduction were PS ≥ 2 , higher CCI values, and larger number of medications. Similarly, early 5-FU discontinuation was independently associated with age 65 to 69 years compared with younger than

65 years (aOR, 3.89; 95% CI, 1.32-11.44; $P=0.01$) but not with age 70 years and older (aOR, 1.84; 95% CI, 0.65-5.2) after adjustment for number of medications (aOR, 1.13; 95% CI, 0.97-1.31; $P=0.113$), BMI (aOR 1-Kg/m² increase, 0.86; 95% CI, 0.77-0.97; $P=0.01$), PS ≥ 2 (aOR, 3.29; 95% CI, 0.76-14.1; $P=0.11$), or CCI (aOR_{1-point increase}, 1.06; 95% CI, 0.81-1.40; $P=0.67$).

Similar factors were associated with 5-FU RDI <0.85 . Defining dose reduction as a 10%, 20%, or 30% decrease instead of a 15% decrease did not change the results (data not shown).

Oxaliplatin

By univariate analysis, compared with the youngest age group, early oxaliplatin discontinuation was more common in the 70 years and older age group ($P=0.01$), whereas no difference was found for the 65- to 69-year age group ($P=0.085$). Similar results were found for RDI (Fig. 2). Other factors associated with oxaliplatin discontinuation were larger number of medications (median, 2 [0 to 5] vs. 1.5 [0 to 3] in the group without early discontinuation, $P=0.07$) and PS ≥ 2 (10.2% vs. 2%; $P=0.07$). CCI was not significantly different between the groups with and without early discontinuation (median, 0 [0 to 2] vs. 1 [0 to 2]; $P=0.83$). No factor was associated with oxaliplatin RDI <0.85 .

The prevalence of neurological toxicity increased with oxaliplatin dose reduction and early oxaliplatin discontinuation, from 24.6% (n=14) in the absence of dose reduction or early discontinuation to 41.2% (n=21) with early discontinuation but no previous dose reduction and 55.6% (n=25) with both dose reduction and early discontinuation.

Survival

Median follow-up was 28.9 months [5.9 to 49.8 mo] and 1-year survival was 85.6%. The proportional hazards assumption was not verified, due to an interaction between time and early discontinuation of 5-FU or oxaliplatin. Therefore, early discontinuation was handled as a time-dependent covariate. In a multivariate model, factors associated with overall 1-year mortality were early 5-FU discontinuation (aHR, 3.1; 95% CI, 1.1-

TABLE 2. Multivariate Analysis of Factors Associated With First-Cycle 5-FU Dose Reduction: The CORSAGE Cohort Study

	Model 1*	<i>P</i> †	Model 2*	<i>P</i> †
	aOR (95% CI)		aOR (95% CI)	
Age (y)				
<65	1	0.03	1	0.03
65-70	5.5 (1.5-19.9)		5.37 (1.36-21.32)	
≥70	2.6 (0.7-9.5)		1.86 (0.47-7.36)	
CCI, 1-point increase	1.4 (1.05-1.82)	0.02	—	
PS = 0	—		1	0.07
PS = 1	—		2.32 (0.83-6.5)	
PS ≥ 2	—		6.02 (1.15-31.4)	
No. medications, 1-point increase	—		1.19 (1.00-1.42)	0.04

*Multivariate analysis using a logistic regression model that included the following variables: age and CCI for model 1; and age, PS, and number of medications for model 2, due to a strong correlation between CCI and number of medications.

†Wald test.

aOR indicates adjusted odds ratio; CORSAGE, COlorectal canceRS, AGe and chemotherapy fEasability study; CCI, Charlson Comorbidity Index; CI, confidence interval; PS, performance status.

8.5; $P=0.027$) and CCI (aHR_{1-point increase}, 1.3; 95% CI, 1.0-1.7; $P=0.03$), but not age (aHR_{1-year increase}, 1.0; 95% CI, 0.98-1.1; $P=0.3$). Early oxaliplatin discontinuation was not associated with overall 1-year mortality by univariate analysis (crude HR, 1.06; 95% CI, 0.4-2.87; $P=0.9$).

DISCUSSION

Main Results

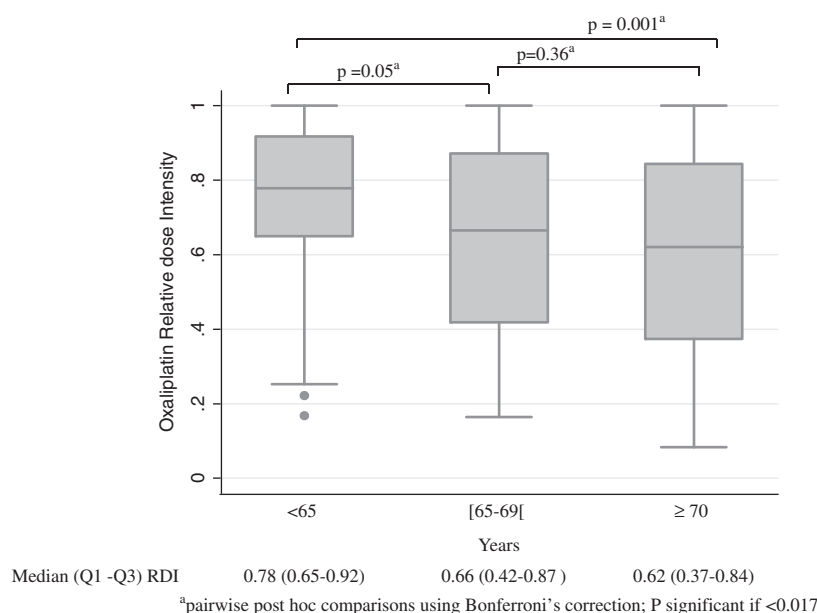
In consecutive patients with stage II or III CRC scheduled for adjuvant-modified FOLFOX6 chemotherapy in the real-life setting, median RDIs were 0.91 for 5-FU and 0.70 for oxaliplatin. Thus, 50% of patients received 91% or more of the planned 5-FU dose and 70% or more of the planned oxaliplatin dose. Our data indicate that middle-aged patients (aged 65 to 69 y) had a higher frequency of 5-FU nonfeasibility as assessed based on first-cycle dose reduction, early discontinuation, and

RDI compared with patients younger than 65 years and to those 70 years or older. These results were unchanged by adjustment for PS, comorbidities, and number of medications.

Dose reduction occurred later for oxaliplatin than for 5-FU, usually about midway through the chemotherapy course, mainly because of toxicities. Oxaliplatin dose reduction was followed by early discontinuation in almost 70% of patients. Oxaliplatin nonfeasibility increased with chronological age.

External Validity

Our study population was comparable in terms of functional status and comorbidities to those included in randomized trials of adjuvant chemotherapy for CRC.²⁷ Our data on the number of cycles received were also similar to those from randomized controlled trials,^{21,28} although patients older than 70 years contributed <10% of the population in these trials compared with 30% in our study.

**FIGURE 2.** Oxaliplatin relative dose intensity (RDI) across age group.

Our study is the first assessment of RDI in CRC patients receiving a homogeneous adjuvant chemotherapy regimen in the real-life setting. Most of the previous studies of RDI were done in patients with breast cancer, non-Hodgkin lymphoma, various solid tumors (mainly breast cancer, CRC, and lung cancer), or metastatic cancer, who required a vast array of chemotherapy regimens. In 3 large retrospective studies of patients with non-Hodgkin lymphoma or breast cancer, 30% to 60% of patients had RDI values <0.85 .^{13,16,22} A study of 108 patients aged 69 years and older with various metastatic solid tumors (mainly lung cancer, CRC, and head-and-neck cancer) showed a mean RDI of 0.76, with a $\geq 20\%$ dose reduction in 28% of patients.²⁹ In an American multicenter study in 976 patients aged 70 years and older with various metastatic solid tumors (mainly lung cancer, CRC, and breast cancer), the overall RDI was 0.8 and 29% of patients had dose reductions $\geq 15\%$,²² in accordance with our results. In a recent Japanese study in CRC patients with metastases who were treated with FOLFOX6, the median oxaliplatin RDI was 0.79.¹⁸

The median RDI in our study was lower in patients aged 65 to 69 years than in younger or older patients, suggesting a U-shaped relationship between age and 5-FU nonfeasibility in patients receiving adjuvant chemotherapy for CRC. This finding was not influenced by adjusting for PS, CCI, or number of medications. It may be ascribable to referral bias, with older patients (≥ 70 y) being referred for combined aggressive combination chemotherapy only when in better general health and with less advanced disease.³⁰ It is in accordance with a recent study of oncologist referral for chemotherapy in 316 CRC patients. Among patients aged younger than 70 years who were eligible for treatment with curative intent, 97% were referred to oncologists for chemotherapy. This high proportion suggests nearly routine referral of relatively young patients to oncologists for adjuvant chemotherapy without a careful assessment of comorbidities and functional status. Such an approach may explain the higher frequency of nonfeasibility in patients aged 65 to 69 years compared with older patients. In the same study, 35% of patients aged 70 years or more were not referred to oncologists, for the following reasons: chemotherapy was deemed inadvisable because of age, comorbidity/physical condition, or lack of expected benefit in 23% of patients, failure to refer to an oncologist despite chemotherapy being deemed advisable in 7% of patients, and patient unwillingness to receive chemotherapy in 5% of patients.³¹ As expected, functional status and comorbidities were associated with chemotherapy nonfeasibility.^{11,32,33}

Number of medications was associated with dose reduction and early discontinuation independently from functional status and CCI. Polypharmacy may raise concern among physicians about side effects,^{8,34} leading to undertreatment of patients older than 65 years, manifesting in part as early dose reduction.⁷ Furthermore, polypharmacy may increase the frequency of drug-drug interactions requiring treatment discontinuation.³⁵

Lower BMI was associated with early 5-FU discontinuation. In earlier studies, the risk of chemotherapy toxicities was higher in patients with low BMI receiving treatment for renal cancer³⁶ or gynecologic cancer.³⁷

Internal Validity

Our study has several strengths. Our population is uniform in terms of the cancer location and chemotherapy regimen. As we included consecutive patients, there was no selection bias. Moreover, the absence of age restrictions to study inclusion enabled a comprehensive analysis of the

association between age and chemotherapy nonfeasibility. In contrast, many earlier studies were confined to older patients.^{29,38,39} Classification bias is unlikely in our study, because chemotherapy doses and times were entered into the hospital chemotherapy database prospectively, in real time, by the nurses and oncologists. We performed a multivariate analysis taking functional status, comorbidities, and number of medications into account.

Our study also has several limitations. The patient recruitment in only 2 centers, both located in teaching hospitals, may affect the general applicability of our findings. However, both centers are public hospitals to which the local populations have full access via French statutory health care insurance. OS was computed based on only 1 year of follow-up, as longer follow-ups were not available; this is a limitation of assessing adjuvant chemotherapy. Finally, whether adding oxaliplatin to 5-FU in patients aged 75 years or older⁵ and whether the optimal duration of oxaliplatin-based adjuvant therapy is 3 or 6 months are points of current controversy. The International Duration Evaluation of Adjuvant Chemotherapy study⁴⁰ for which recruitment is under way, should provide answers to the second point.

Clinical Implications

The International Society of Geriatric Oncology recommends a Comprehensive Geriatric Assessment (CGA) in all patients with cancer aged 70 years or older.⁴¹ A CGA may also be useful for patients aged 65 to 69 years who are considered for chemotherapy but have predictors of nonfeasibility, such as polypharmacy/comorbidities or functional impairments. Indeed, compared with chronological age alone, CGA findings may provide better guidance⁴²⁻⁴⁵ for selecting the initial chemotherapy dose and may identify interventions designed to improve potentially modifiable frailty parameters.¹¹

Further studies involving the collection of more detailed patient characteristics are needed to confirm or disprove the suggested U-shaped relation between 5-FU chronological age and nonfeasibility.

CONCLUSIONS

In patients with stage II or III CRC scheduled to receive adjuvant-modified FOLFOX6 chemotherapy in the real-life setting, median RDIs were 0.91 for 5-FU and 0.70 for oxaliplatin. Compared with their younger counterparts, patients aged 65 to 69 years had higher frequencies of 5-FU nonfeasibility defined based on first-cycle dose reduction, early discontinuation, and RDI, independently from PS, comorbidities, and number of medications. Contrary to 5-FU dose reduction, oxaliplatin dose reductions usually occurred mid-way through the chemotherapy course; these reductions were mainly due to toxicities and were followed by early discontinuation in almost 70% of cases. Oxaliplatin nonfeasibility increased with chronological age.

ACKNOWLEDGMENTS

The authors thank Antoinette Wolfe, MD, for editing the manuscript. They are also indebted to Louis-Félix Ozier-Lafontaine for clinical research support.

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