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BRIEF REPORT
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Exploratory study on relative dose intensity and reasons for dose reduction of adjuvant CAPOX therapy in elderly patients with colorectal cancer

Ayumi Tsuchiya[1,*], Chiaki Ogawa[1], Naoki Kondo[1], Yasushi Kojima[2], Yasuhide Yamada[3], Hiroyuki Terakado[1]

[1] Pharmaceutical Department, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan;
[2] Gastroenterology, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan;
[3] Comprehensive Cancer Center, Center Hospital of the National Center for Global Health and Medicine, Tokyo, Japan.

Abstract: Capecitabine plus oxaliplatin, CAPOX, therapy is one of the standardized options for adjuvant chemotherapy for colorectal cancer, but the efficacy and the safety of CAPOX in elderly patients are unclear. In this study, we investigated the relative dose intensity (RDI) and reasons for dose reduction in patients over the age of 70 (elderly group) (n = 12) and those under the age of 70 (non-elderly group) (n = 24) receiving adjuvant CAPOX therapy for colorectal cancer. The median RDIs were 71.1% in the elderly group and 67.9% in the non-elderly group for oxaliplatin (p = 0.416), and 81.6% and 86.4% for capecitabine (p = 0.166), respectively. The rate of peripheral neuropathy which was the reason for dose reduction of oxaliplatin was approximately 4.5-fold higher in the non-elderly group than in the elderly group. In addition, hematologic toxicity was the most common reason for dose reduction at 50.0% in the elderly group. The results of this study suggested that a similar therapeutic intensity can be maintained in elderly patients relative to non-elderly patients by appropriate dose reduction and discontinuation of drug treatments. Elderly patients are more susceptible to hematologic toxicity than to peripheral neuropathy.

Keywords: oxaliplatin, over the age of 70, therapeutic intensity, peripheral neuropathy, hematologic toxicity

Introduction

Cancer has been the leading cause of death in Japan since 1981. According to the latest cancer statistics from the Center for Cancer Control and Information Services, National Cancer Center, colorectal cancer was the most common cancer in 2017, and its age-adjusted incidence rate in people over the age of 70 was 59% in 2015, accounting for more than half of the total incidence rate (*1*).

Surgery and adjuvant chemotherapy are regarded as the standard treatment for resectable colorectal cancer. CAPOX therapy, a combination of capecitabine and oxaliplatin, has been shown to be superior to fluorouracil (FU) + levofolinate calcium (*l*-LV) therapy in terms of disease-free survival (DFS) (*2*). It has become one of the standardized options for adjuvant chemotherapy for colorectal cancer in Japan.

Adjuvant chemotherapy with an FU-based regimen has been shown to be effective regardless of age; however, the results of clinical trials evaluating the efficacy of the combined use of oxaliplatin are still controversial (*3-5*), and consistent results have not been obtained (*6*). Furthermore, peripheral neuropathy arises in a dose-dependent manner when oxaliplatin is used in combination (*7,8*). There are only a few reports of adverse events in patients over the age of 70 that have been investigated to date, and they are often excluded from clinical trials because of worse performance status or complications. The Clinical Practice Guidelines of Cancer Drug Therapies for the Elderly (*9*) stipulate that "adjuvant chemotherapy may be considered for elderly patients with good performance status and organ function and no serious complications", but the efficacy and the safety of the CAPOX therapy in patients over the age of 70 have not been clarified.

In this study, we investigated the relative dose intensity (RDI) and reasons for dose reduction in patients over the age of 70 and those under the age of 70 receiving adjuvant CAPOX therapy for colorectal cancer.

Patients and Methods

Patients

Patients over the age of 18 who started CAPOX therapy as adjuvant chemotherapy for colorectal cancer at the Center Hospital of the National Center for Global

Health and Medicine (NCGM) between January 2018 and August 2019 were included. Surgery was performed on all patients within 8 weeks. Of these patients, those who met the criteria of white blood cells ≥ 3,000/mm^3, neutrophils ≥ 1,500/mm^3, platelets ≥ 75,000/mm^3, hemoglobin ≥ 8.0 mg/dL, total bilirubin ≤ 1.5 mg/dL, and serum creatinine ≤ 1.5 mg/dL at the start of treatment were included. Other eligibility criteria included an Eastern Cooperative Oncology Group Performance Status of 0/1. Patients with known peripheral neuropathy were excluded.

Methods

CAPOX therapy consisted of 8 courses of treatment with each course as a 21-day cycle, administering 130 mg/m^2 oxaliplatin on day 1 and 2,000 mg/m^2 capecitabine per day from after dinner on day 1 to after breakfast on day 15.

A retrospective survey was conducted based on electronic medical records. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0 (CTCAE ver.5.0). The RDI was calculated as (Actual total dose/Actual total administration period)/(Planned total dose/Planned total administration period) × 100 (%). Based on the Guidelines for the Treatment of Colorectal Cancer, "elderly" was defined as over the age of 70. Patients over the age of 70 (elderly group) was compared with those under the age of 70 (non-elderly group).

Baseline characteristics of patients, course of treatment, RDI (%), reasons for dose reduction and discontinuation of oxaliplatin, and reasons for dose reduction of capecitabine were investigated.

Statistical analysis

The Mann-Whitney *U* test was used to compare quantitative data, and the chi-square test or the Fisher's exact test was used to compare qualitative data. In all cases, $p < 0.05$ was considered a statistically significant difference. IBM SPSS® Statistics ver.24 was used for all statistical analyses.

Ethical conduct of the study

This study was conducted with the approval of the Ethical Review Committee of NCGM (Approval number: NCGM-G-003546-01), in compliance with the "Ethical Guidelines for Medical and Health Research Involving Human Subjects" and paying the utmost attention to the protection of personal information.

Results and Discussion

Baseline characteristics of the study patients

The baseline characteristics of the 36 patients are shown in Table 1. The median age of the 12 elderly patients and the 24 non-elderly patients was 74.0 and 52.0, respectively. Laboratory data prior to the start of treatment indicated that hemoglobin and albumin were significantly lower in the elderly than in the non-elderly group ($p = 0.026$ and 0.022, respectively).

Course of treatment

The courses of treatment for the 36 patients are shown in Figure 1. In total, 69.4% of the patients (25/36) completed the 8 courses. The rate of treatment completion in the elderly group ($n = 12$) and the non-elderly group ($n = 24$) was 58.3% (7/12) and 75.0% (18/24), respectively. The reasons for failure to complete treatment in the elderly-vs-non-elderly groups were recurrence in 1 and 4 patients; concomitant other diseases or progression of other diseases such as lung cancer in 4 and 0 patients; financial considerations in 0 and 1 patient; and a personal decision in 0 and 1 patient, respectively.

Relative dose intensity (RDI) of CAPOX

The median RDIs in the elderly and non-elderly patients who completed the 8 courses are shown in Figure 2. The RDIs of oxaliplatin were 71.1% and 67.9%, respectively (not significant, $p = 0.416$) and the RDIs of capecitabine were 81.6% and 86.4%, respectively (also not significant, $p = 0.166$).

Reasons for dose reduction or discontinuation of oxaliplatin and capecitabine

The reasons for dose reduction and discontinuation of oxaliplatin are shown in Table 2 and the reasons for dose reduction of capecitabine are shown in Table 3. The rate of peripheral neuropathy which was the reason for dose reduction of oxaliplatin was 8.3% (1/12) in the elderly group but approximately 4.5-fold higher in the non-elderly group (37.5%; 9/24). All patients discontinuing oxaliplatin due to peripheral neuropathy were in the non-elderly group, accounting for 29.2% (7/24), with a median number of 6 oxaliplatin courses. In addition, in the elderly group, the most common reason for dose reduction of oxaliplatin was hematologic toxicity in 50.0% of the patients (6/12).

Discussion

The actual condition of treatment in patients over the age of 70 who were treated with adjuvant CAPOX therapy for colorectal cancer at NCGM is reported here. The rate of treatment completion was lower in the elderly group than in the non-elderly group, but not all reasons for failure to complete treatment were due to adverse events. In addition, there was no difference in

Table 1. Baseline characteristics of patients

Characteristic	Elderly (n = 12)	Non-Elderly (n = 24)	P value
Age, years			
Median (Range)	74.0 (70.0-77.0)	52.0 (27.0-67.0)	
Sex			0.451
Male	7 (58.3%)	17 (70.8%)	
Female	5 (41.7%)	7 (29.2%)	
Body surface area, m^2			
Average ± SD	1.60 ± 0.167	1.70 ± 0.174	0.128
ECOG-PS			1.000
0/1/2/3/4	9/3/0/0/0	18/6/0/0/0	
Laboratory data			
White blood cell ($\times 10^3/mm^3$)	5.73 ± 1.04	5.74 ± 2.13	0.728
Neutrophil ($\times 10^3/mm^3$)	3.71 ± 1.21	3.64 ± 1.74	0.497
Hemoglobin (g/dL)	11.2 ± 2.50	12.8 ± 1.84	0.026
Platelet ($\times 10^4/mm^3$)	27.2 ± 8.68	29.1 ± 12.4	0.753
Total bilirubin (mg/dL)	0.555 ± 0.202	0.546 ± 0.277	0.908
Serum creatinine (mg/dL)	0.754 ± 0.207	0.798 ± 0.196	0.361
Albumin (g/dL)	3.92 ± 0.397	4.23 ± 0.493	0.022
Site			
Ascending colon	4 (33.3%)	1 (4.17%)	
Transverse colon	2 (16.7%)	0 (0%)	
Descending colon	0 (0%)	3 (12.5%)	
Sigmoid colon	3 (25.0%)	6 (25.0%)	
Rectum	1 (8.33%)	10 (41.7%)	
Cecum	2 (16.7%)	2 (8.33%)	
Appendix vermiformis	0 (0%)	2 (8.33%)	
Stage			
IIIa	2 (16.7%)	5 (20.8%)	
IIIb	6 (50.0%)	9 (37.5%)	
IIIc	1 (8.33%)	4 (16.7%)	
IV (liver metastasis)	3 (25.0%)	4 (16.7%)	
unclear	0 (0%)	2 (8.33%)	

SD: standard deviation, ECOG-PS: Eastern Cooperative Oncology Group Performance Status.

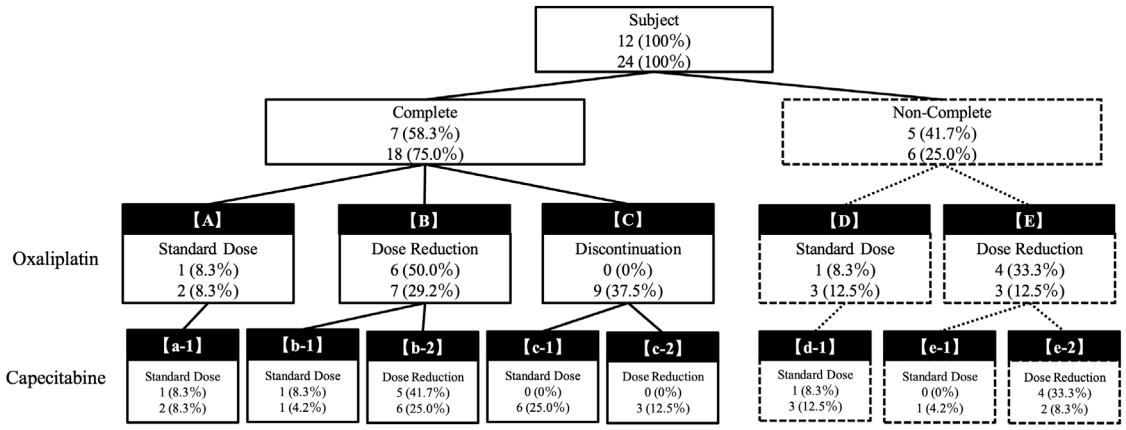

Figure 1. Course of treatment. Upper row; Elderly, Lower row; Non-Elderly. **(A)**: Oxaliplatin Standard Dose, Complete. **(B)**:Oxaliplatin Dose Reduction, Complete. **(C)**:Oxaliplatin Discontinuation, Complete. **(D)**:Oxaliplatin Standard Dose, Non-Complete. **(E)**:Oxaliplatin Dose Reduction, Non-Complete. **(a-1)**:(A) and Capecitabine Standard Dose, Complete. **(b-1)**:(B) and Capecitabine Standard Dose, Complete. **(b-2)**:(B) and Capecitabine Dose Reduction, Complete. **(c-1)**:(C) and Capecitabine Standard Dose, Complete. **(c-2)**:(C) and Capecitabine Dose Reduction, Complete. **(d-1)**:(D) and Capecitabine Standard Dose, Non-Complete. **(e-1)**:(E) and Capecitabine Standard Dose, Non-Complete. **(e-2)**:(E) and Capecitabin Dose Reduction, Non-Complete.

RDIs between the two groups for either oxaliplatin or capecitabine in patients who completed the 8 courses. These results suggest that it is possible to complete treatment while maintaining the therapeutic intensity even in patients over the age of 70. On the other hand, discontinuation of treatment due to concomitant other diseases or progression of other diseases was more frequent in the elderly group, suggesting that it is necessary to intervene with elderly patients, paying attention not only to the occurrence of adverse

events but also to the complications that may require discontinuation of treatment.

Anemia, hypoalbuminemia, hypomagnesemia, and habit of alcohol consumption are known to be risk factors for peripheral neuropathy, especially in oxaliplatin-treated patients (*10*). In the present study, hemoglobin and albumin levels prior to the start of treatment were significantly lower in the elderly group. In addition, serum magnesium levels were often not included in the laboratory data prior to the start of treatment, and there were cases in which there were no medical records regarding alcohol consumption. Therefore, characteristics of the patients in this study were insufficient to confirm the risk factors for peripheral neuropathy. The hemoglobin and albumin levels suggest that the risk of peripheral neuropathy is high in the elderly group. However, the effects of peripheral neuropathy were lower in the elderly group than in the non-elderly group in the results of this survey; thus, we investigated the effects of age on peripheral neuropathy.

There have been several reports of the age-specific risks of oxaliplatin-induced peripheral neuropathy. A study comparing patients with colorectal cancer

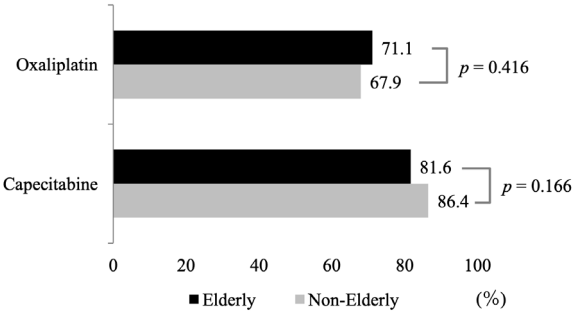

Figure 2. Median relative dose intensities (RDIs) in patients completed 8-courses. The median RDIs of oxaliplatin were 71.1% in the elderly and 67.9% in the non-elderly ($p = 0.416$). The RDIs of capecitabine were 81.6% and 86.4%, respectively ($p = 0.166$).

Table 2. Reasons for dose reduction and discontinuation of oxaliplatin

Reason	Dose Reduction									Discontinuation							
	Elderly (n = 12)				Non-Elderly (n = 24)				P value	Elderly (n = 12)				Non-Elderly (n = 24)			
	All Grade		Grade ≥ 3		All Grade		Grade ≥ 3			All Grade		Grade ≥ 3		All Grade		Grade ≥ 3	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)		No.	(%)	No.	(%)	No.	(%)	No.	(%)
Hematologic toxicity	6	(50.0)	2	(16.7)	6	(25.0)	3	(12.5)	0.157	0	(0)	0	(0)	2	(8.3)	1	(4.2)
Neutropenia	3	(25.0)	0	(0)	5	(20.8)	3	(12.5)	1.000	0	(0)	0	(0)	1	(4.2)	1	(4.2)
Thrombocytopenia	5	(41.7)	2	(16.7)	3	(12.5)	0	(0)	0.086	0	(0)	0	(0)	1	(4.2)	0	(0)
Non-Hematologic toxicity	4	(33.3)	2	(16.7)	14	(58.3)	5	(20.8)	0.157	0	(0)	0	(0)	7	(29.2)	2	(8.3)
Peripheral neuropathy	1	(8.3)	0	(0)	9	(37.5)	2	(8.3)	0.115	0	(0)	0	(0)	7	(29.2)	2	(8.3)
Anorexia	2	(16.7)	1	(8.3)	1	(4.2)	0	(0)	0.253	0	(0)	0	(0)	0	(0)	0	(0)
Diarrhea	1	(8.3)	1	(8.3)	4	(16.7)	2	(8.3)	0.646	0	(0)	0	(0)	0	(0)	0	(0)
Nausea	0	(0)	0	(0)	2	(8.3)	0	(0)	0.543	0	(0)	0	(0)	0	(0)	0	(0)
Malaise	0	(0)	0	(0)	1	(4.2)	1	(4.2)	1.000	0	(0)	0	(0)	0	(0)	0	(0)
Infection	1	(8.3)	0	(0)	1	(4.2)	0	(0)	1.000	0	(0)	0	(0)	0	(0)	0	(0)

There is some overlapping. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0. The worst grade considered at least possibly related to treatment is given. The P values are for the differences between the groups for all grades.

Table 3. Reasons for dose reduction of capecitabine

Reason	Elderly (n = 12)				Non-Elderly (n = 24)				P value
	All Grade		Grade ≥ 3		All Grade		Grade ≥ 3		
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	
Hematologic toxicity	4	(33.3)	2	(16.7)	5	(20.8)	3	(12.5)	0.443
Neutropenia	1	(8.3)	0	(0)	4	(16.7)	3	(12.5)	0.646
Thrombocytopenia	3	(25.0)	2	(16.7)	2	(8.3)	0	(0)	0.307
Non-Hematologic toxicity	6	(50.0)	2	(16.7)	7	(29.2)	3	(12.5)	0.281
Anorexia	1	(8.3)	0	(0)	1	(4.2)	0	(0)	1.000
Diarrhea	1	(8.3)	1	(8.3)	4	(16.7)	2	(8.3)	0.646
Hand-foot syndrome	3	(25.0)	1	(8.3)	2	(8.3)	1	(4.2)	0.307
Infection	1	(8.3)	0	(0)	0	(0)	0	(0)	0.333

There is some overlapping. The severity of adverse events was assessed according to the Common Terminology Criteria for Adverse Events, version 5.0. The worst grade considered at least possibly related to treatment is given. The P values are for the differences between the groups for all grades.

aged 50 to 68 years with those over the age of 69 who were treated with adjuvant chemotherapy or first-line treatment for metastatic disease reported no age-associated statistically significant difference in acute or chronic peripheral neuropathy (*11*). On the other hand, in a study of patients with colorectal cancer who were treated with adjuvant chemotherapy, the risk of peripheral neuropathy was reported to be higher in patients over the age of 70 than in those aged 66 to 69 years (*12*). It has also been reported that the duration of peripheral neuropathy was longer in patients under the age of 60 than in those over the age of 60 (*10*). Thus, there is no consensus on the risks of oxaliplatin-induced peripheral neuropathy with respect to age.

The effects of peripheral neuropathy were lower in the elderly group than in the non-elderly group in our study. The reason for this may be due to the effect of hematologic toxicity. In the elderly group, hematologic toxicity was the reason for 50.0% of all cases of oxaliplatin dose reductions. In the elderly, the decline in bone marrow function associated with aging may lead to more severe hematologic toxicity and prolonged recovery (*13*). In the present study, there was no significant difference between the elderly and non-elderly groups in the blood cell counts prior to the start of CAPOX therapy except for the hemoglobin level. This suggests that elderly patients may have been more susceptible to hematopoietic exhaustion due to chemotherapy, and may have experienced less peripheral neuropathy due to dose reduction resulting from hematologic toxicity in response to more severe hematologic toxicity and prolonged recovery before the reduction resulting from peripheral neuropathy.

The limitations of this study include the small number of cases; hence, further research is needed on a larger number of patients. Second, we were unable to evaluate efficacy in terms of overall survival or disease-free survival, because there has been insufficient time since completing adjuvant CAPOX therapy. In addition, it was not possible to retrospectively investigate patient adherence with capecitabine, which is an oral anticancer drug. The RDI for capecitabine was calculated based on the number of prescription days, and the RDI may possibly be even lower in patients with poor adherence. Especially in the elderly, who are often treated by polypharmacy due to chronic diseases, in addition to a decline in activities of daily living and cognitive function (*13*), it is important to ensure adherence in order to maintain the therapeutic intensity of CAPOX therapy. In future, it will be necessary to consider including a survey of adherence.

In conclusion, the results of this study suggested that a similar therapeutic intensity can be maintained in elderly patients relative to non-elderly patients by appropriate dose reduction and discontinuation of drug treatments. Elderly patients are more susceptible to hematologic toxicity than to peripheral neuropathy.

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Conflict of Interest: Y.Y. has received honoraria from Chugai, Taiho, and Nipponkayaku, Japan. The other authors declare that they have no conflicts of interest.

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Address correspondence to:
Ayumi Tsuchiya, Pharmaceutical Department, Center Hospital of the National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: atsuchiya@hosp.ncgm.go.jp