Grade 3/4 neutropenia is a limiting factor in second-line FOLFIRI following FOLFOX4 failure in elderly patients with metastatic colorectal cancer

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Abstract. Previous studies have reported improved outcomes for elderly patients with metastatic colorectal cancer (mCRC) treated with oxaliplatin or irinotecan as first-line chemotherapy. However, few studies regarding second-line chemotherapy with oxaliplatin or irinotecan are currenlty available. We analyzed retrospectively the efficacy and toxicity in elderly patients (median age, 74 years) treated with second-line FOLFIRI following first-line FOLFOX4 failure. From March 2005 to January 2008, 35 elderly patients with mCRC received first-line FOLFOX4 comprising leucovorin, 5-FU and oxaliplatin followed by second-line FOLFIRI comprising leucovorin, 5-FU and irinotecan. The median number of treatment courses with FOLFIRI was 5 (range 2-32). One patient responded to the treatment. The disease control rate was 38.2%. The median time to treatment failure was 3 months, and the median overall survival (OS) time from the beginning of first-line chemotherapy was 20.7 months. The incidence of grade 3/4 neutropenia was 71.4%, while febrile neutropenia was 11.4%. The incidence of non-hematological toxicity was low. The use of the three active drugs, 5-FU, oxaliplatin and irinotecan, in mCRC produced the longest OS in elderly as well as in younger patients. However, the elderly patients treated with second-line FOLFIRI had a high rate of hematological toxicity. Second-line FOLFIRI may therefore be used with caution in the elderly.

Introduction

Colorectal cancer (CRC) is one of the most common neoplasms in elderly patients. Currently, the median age at diagnosis of colorectal cancer in the United States is 72 years, in Europe 74 years, and in Japan, the late 60s (1). The incidence of colorectal cancer increases with age. As the world's population is aging, providing optimal care for elderly patients with CRC is highly relevant.

Findings of a previous study showed that making three active drugs (5-FU, irinotecan and oxaliplatin) available to any patient with advanced CRC who is a candidate for such therapy maximizes overall survival (OS) (2). In the metastatic setting, the case for the benefits of chemotherapy is compelling as CRC survival without treatment is only 6 months, exceeding 20 months for patients treated with chemotherapy with combination regimens, such as FOLFOX, FOLFIRI and XELOX, and currently exceeding 24 months when chemotherapy is supplemented with biological agents, such as bevacitumab, cetuximab and panitumumab (3). However, the use of palliative chemotherapy for metastatic CRC (mCRC) also appears to decline with patient age. Although 70% of patients younger than 70 receive some chemotherapy for metastatic CRC, only 43% of patients older than 70 receive palliative chemotherapy (4).

Aging is often associated with physiological, sociological and psychological changes. One of the hallmarks of aging is gradual loss of physiologic reserve involving loss of the body's ability to compensate when exposed to stressors such as infection, cancer and chemotherapy (5,6). Declining reserves results in a gradual decline in normal organ function. For example, glomerular filtration rate, cardiac motility, hepatic volume, and blood flow all decline with age, as does immunologic and hematologic function (7,8). Each of these changes has the potential to increase the risk and decrease the tolerance to adverse effects from chemotherapeutics. Therefore, elderly patients presenting with CRC are often under-represented or excluded from clinical trials. Occasionally, selected elderly patients have been treated with chemotherapy in clinical trials. These selected elderly patients have few comorbidities, given their excellent performance status and organ function (9). To address this issue, multiple pooled analyses and meta-analyses have been conducted, all of which have concluded that the efficacy and toxicity of CRC chemotherapy among younger and older patients who were in good health and were willing to enroll in clinical trials were essentially equivalent.

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In 2001, a pooled analysis of seven trials randomly assigning patients to fluorouracil (FU) with leucovorin (LV) or levamizole versus observation in an adjuvant setting found no association between age and the effect of treatment on disease-free survival or OS, suggesting equal efficacy of chemotherapy in the elderly (10). Combination chemotherapy also appears to be beneficial in healthy older patients. Results of pooled analyses of both oxaliplatin- and irinotecan-based regimens have been found to be the same as those of FU trials (11-13). In contrast, in a smaller phase III trial that compared weekly versus every-third-week irinotecan, patients >70 years of age had significantly increased odds of suffering grade 3 or 4 diarrhea and neutropenia than younger patients (14). Thus, the extent to which older patients treated with irinotecan have an increased risk of toxicity warrants further investigation. Given the current evidence, the use of oxaliplatin- and irinotecan-based regimens (FOLFOX, FOLFIRI and XELOX) as first-line chemotherapy in healthy elderly patients may be feasible.

However, data concerning the effect of three active cytotoxic agents on OS and safety in elderly patients are not yet available. Additionally, no data from clinical trials are currently available regarding chemotherapy using first-line FOLFOX4 followed by second-line FOLFIRI in elderly patients. Therefore, we analyzed retrospectively and reported the results of the tolerance and efficacy of second-line FOLFIRI for mCRC in elderly patients treated at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

Patients and methods

Patients. Data were collected retrospectively from medical records available from 35 patients treated at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Our analysis of outcome data included all patients over 70 years of age treated with second-line FOLFIRI from March 2005 to January 2008 following first-line FOLFOX4 failure for mCRC. All patients had histologically confirmed colorectal adenocarcinoma.

Treatment plan. The chemotherapy regimens used were first-line FOLFOX4 (LV 200 mg/m^2/day as a 2-h infusion followed by bolus 5-FU 400 mg/m^2/day and a 22-h 5-FU infusion of 600 mg/m^2/day, repeated for 2 consecutive days every 2 weeks; 85 mg/m^2 of oxaliplatin was administered on day 1 as a 2-h infusion concurrent with LV) and second-line FOLFIRI (LV 200 mg/m^2/day as a 2-h infusion followed by bolus 5-FU 400 mg/m^2/day and a 46-h 5-FU infusion of 2400 mg/m^2/day, every 2 weeks; 150 mg/m^2 of irinotecan was administered on day 1 as a 1.5-h infusion concurrent with LV).

According to evidence-based medicine, treatment was continued until disease progression or unacceptable toxicity occurred or until the patient chose to discontinue treatment.

Evaluation of efficacy and toxicity. Patients were evaluated for adverse events prior to each cycle and graded according to NCI Common Toxicity Criteria (version 3.0). When measurable, tumor response was assessed using computed tomography (CT) approximately every 3 months according to the Response Evaluation Criteria in Solid Tumors criteria (RECIST) (15). Treatment outcome was determined by OS and time to treatment failure (TTF). OS was calculated from the beginning of first-line chemotherapy until documentation of death. TTF was defined as the time from the beginning of second-line chemotherapy to the progression or failure of treatment or the patient succumbing due to any cause.

Table I. Baseline characteristics at the beginning of second-line chemotherapy.

Characteristics	No. of patients
Total no. of patients	35
Age (years)	
Median	74
Range	71-77
Gender	
Male	18 (51.4%)
Female	17 (48.6%)
ECOG performance status	
0	23 (65.7%)
1	12 (34.3%)
Primary tumor site	
Colon	21 (60%)
Rectum	14 (40%)
Number of metastatic sites	
1	9 (25.7%)
>1	26 (74.3%)
Adjuvant chemotherapy	
Yes	16 (45.7%)
No	19 (54.3%)
Charlson comorbidity index	
0	24 (68.6%)
1	9 (25.7%)
2	2 (5.7%)
Clinical history	
Hypertension	11 (31.4%)
Diabetes mellitus	1 (2.8%)
Thromboembolic disease	1 (2.8%)
Heart disease	2 (5.7%)
Another cancer	3 (8.6%)

Statistical analysis. OS and TTF were calculated using the Kaplan-Meier method. Multivariate logistic regression stepwise models were used to explore the correlation between the incidence of severe hematological toxicity (grade 3 and 4 neutropenia) and age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), comorbidity, number of first-line FOLFOX4 cycles received, number of metastatic locations, relative dose intensity values in second-line FOLFIRI and presence of adjuvant treatment. Data were analyzed using the SPSS package version 17.0 (SPSS Inc., Chicago, IL) and two-sided $P<0.05$ were considered to be statistically significant.

Table II. Efficacy and toxicities in first-line FOLFOX4.

First-line result, % (95% CI)	
Objective response rate	31.4 (16.1-46.7%)
Disease control rate	62.8 (46.8-78.8%)
Median PFS in months	6.0 (5.4-6.5)
Range	2.8-10.5
Reasons for discontinuing treatment, (n, %)	
Disease progression	25 (71.4)
Neurotoxicity	3 (8.6)
Allergy	7 (20.0)
Hematological toxicity (grade ≥3), (n, %)	
Leukopenia	4 (11.4)
Neutropenia	20 (57.1)
Anemia	1 (2.8)
Febrile neutropenia	1 (2.8)

CI, confidence interval; PFS, progression-free survival.

Table III. Most common drug-related adverse events in FOLFIRI.

Grade ≥3 toxicity	No.	%
Any drug-related adverse event	29	82.8
Neutropenia	25	71.4
Leukopenia	16	45.7
Anemia	1	2.8
Febrile neutropenia	4	11.4
Infection	1	2.8
Diarrhea	1	2.8
Nausea/Vomiting	3	8.6
Anorexia	1	2.8
Mucositis	3	8.6
Hepatic toxicity	1	2.8

Results

Patient characteristics. Patient characteristics are shown in Table I. The median age was 74 years (range 71-77). All 35 patients had a favorable ECOG PS of 0 or 1. Eleven patients were metastatic at the time of diagnosis. The main metastatic locations were the liver (63%), lung (63%), and lymph nodes (57%). A total of 18 patients received prior adjuvant FU-based chemotherapy. In total, 19 patients (54%) experienced comorbidity, mainly hypertension, diabetes, ulcer disease or another type of cancer. Comorbidity was present in 11 (31%) patients when using the Charlson comorbidity index (CCI) (Charlson *et al,* 1987). All 35 patients received FOLFOX4 regimen as the first-line treatment. A total of 394 cycles of treatment with FOLFOX4 regimen were administered, with a median of 10 cycles per patient (range 5-26 cycles). The efficacy and toxicity in the patients receiving first-line FOLFOX4 are listed in Table II.

Treatment duration of FOLFIRI. A total of 279 cycles of treatment were administered, with a median of 5 cycles per patients (range 2-37 cycles). Nine patients (26%) required a dose reduction, usually for hematologic toxicity (78%). Seven patients started with a lower dose (irinotecan 120 mg/m^2, bolus 5-FU 320 mg/m^2 and 5-FU infusion 1920 mg/m^2) after undergoing a dose reduction due to hematologic toxicity with prior chemotherapy. The median relative dose-intensity values were 81.6% for CPT-11. Treatment was discontinued due to non-progression of disease in 10 (29%) patients; 4 of them with worsening PS. Other reasons for discontinuation included interstitial lung disease in 2 patients, febrile neutropenia (FN) in 3 patients (these patients refused treatment), and treatment-related death in 1 patient. Five patients (14%) discontinued treatment before the first evaluation of response was performed. The reasons were interstitial lung disease in 2 patients, FN in 2 patients, and death in 1 patient.

Toxicity of FOLFIRI. In total, 29 (83%) patients experienced grade 3 and 4 toxicity (Table III). The main severe toxicities were neutropenia in 25 (71%) patients and leukopenia in 16 (46%) patients. Four (11%) patients had FN. However, these patients experienced less non-hematological toxicity. Three (9%) patients had grade 3 mucositis, 3 (9%) patients had grade 3 nausea and vomiting, and 2 (6%) patients had grade 3 anorexia. Only one patient had diarrhea. There was 1 treatment-related death due to grade 3 hyponatremia. No patient experienced worsening comorbidity.

In an exploratory multivariate analysis, the presence of severe neutropenia (grade 3 and 4) in first-line FOLFOX4 was associated with a significant increase in the presence of grade 3 and 4 neutropenia in second-line FOLFIRI (P=0.049, Table IV). However, no significant correlation was observed between the presence of grade 3 and 4 neutropenia in second-line FOLFIRI and patient age (70-74 vs. ≥75 years), gender, PS (0 vs. 1), comorbidity (CCI 0 vs. ≥1), number of first-line FOLFOX4 cycles (9 vs. >9), number of metastatic locations (1 vs. >1), relative dose intensity values in second-line FOLFIRI (<80 vs. ≥80) or presence of adjuvant treatment (yes vs. no).

Efficacy of FOLFIRI. A total of 30 patients were considered to be assessable for response. The best objective responses were achieved as follows: non-complete response (CR), 1 (3.3%) partial response (PR), 12 (40%) stable diseases (SD) and 17 (57%) treatment failures.

Figs. 1 and 2 show the TTF in second-line FOLFIRI and OS from the beginning of first-line chemotherapy, respectively. After a median follow-up of 19.5 months (range 5.8-43.5) at the time of analysis, all 35 patients experienced treatment failure, and 25 patients succumbed to the disease. We were unable to follow up 5 patients after their disease progression. The median TTF in second-line FOLFIRI was 3.0 months (95% CI, 1.2-4.7 months), and the median OS time from the commencement of the first-line chemotherapy was 20.7 months (95% CI, 18.9-22.5 months). No patients had undergone surgery. Among the patients who progressed to further chemotherapy, third-line treatment was administered

Table IV. Multivariate analysis of the association between severe neutropenia in second-line FOLFIRI and patient characteristics.

Outcome	Estimate	SE	OR	95% CI	P-value
Severe neutropenia in first-line FOLFOX4	1.601	0.812	4.958	1.009-24.370	0.049

SE, standard error; CI, confidence interval.

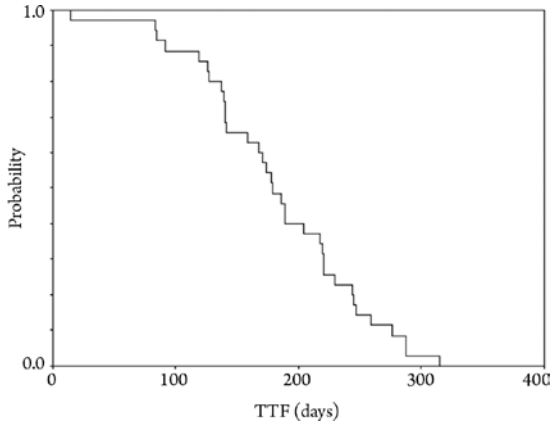

Figure 1. Time to treatment failure (TTF) in second-line FOLFIRI.

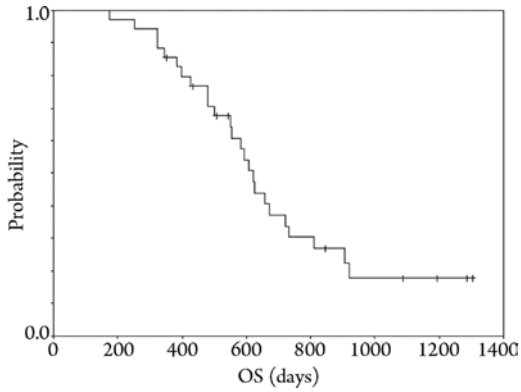

Figure 2. Overall survival (OS) from beginning of first-line FOLFOX4 chemotherapy.

to 6 (17%) patients. This comprised cetuximab-based regimens in 3 patients (not assessed for KRAS mutation status) and hepatic arterial infusion chemotherapy in 3 patients. Few patients received third-line chemotherapy for the reason that cetuximab and panitumunab were not approved in Japan until June 2008.

Discussion

The modern era of combination chemotherapy commenced when it was shown that irinotecan prolonged median OS in patients resistant to 5-FU (16). Since then, the use of combination chemotherapy, both as first- and second-line, has increased life expectancy by nearly two years. OS is correlated with the percentage of patients who receive the three agents of 5-FU, irinotecan and oxaliplatin. Consequently, the use of first- and second-line combination chemotherapy confirms the assumption that more patients should be exposed to the three key drugs (2).

An oxaliplatin-based investigation pooled the results of patients of 70 years of age or older who were treated with oxaliplatin with infusional FU and LV (FOLFOX) for mCRC in three clinical trials and in one adjuvant trial (11). The rate of hematologic toxicity was statistically significantly higher in this group of older patients, although absolute differences between the age cohorts were small. The incidence of non-hematologic grade 3 or 4 toxicity was similar across age groups. The results of the pooled and pre-trial analyses showed that the response rate, disease-free survival and OS were not affected by age. In addition, the irinotecan-based investigation pooled data from 1484 patients, 303 (20%) of whom were 70 years or older, in three randomized trials comparing irinotecan/FU/LV with FU/LV in first-line therapy. No difference was found in the response rate, time to progression, or survival with regards to age for patients treated with FU/LV or irinotecan/FU/LV. Additionally, no difference was noted in the incidence of any grade 3 or 4 toxicity between age group in patients treated with irinotecan combinations (17).

A shorter survival was noted in elderly patients when the proportion of patients who received second-line chemotherapy was low. Subsequently, irinotecan was not widely used as a second-line therapy (18). Therefore, it may be necessary to increase the proportion of elderly to whom second-line treatment is administered following disease progression. However, the majority of the previously mentioned systematic reviews only include studies that evaluate first-line palliative chemotherapy (19). Therefore, it is unclear from our evidence whether combination second-line chemotherapy with elderly patients is safe and efficacious.

The present study aimed to analyze the efficacy and safety of a second-line FOLFIRI regimen (following first-line FOLFOX4 failure) in elderly patients (≥70 years of age) with mCRC. Our results, with a response rate of 3.3%, a median progression-free survival (PFS) of 3.0 months, and a median OS of 20.7 months were similar to those obtained in a previous study with first-line FOLFOX4 followed by second-line FOLFIRI that included patients aged <70 years (22). Our results suggest that the use of all three active drugs in mCRC produces the longest OS in elderly patients (≥70 years) as well as in younger ones.

However, second-line FOLFIRI regimen following first-line FOLFOX4 may not be entirely safe. In total, 83% of the patients experienced grade 3/4 adverse events, particularly severe neutropenia (grade 3/4), and the incidence of FN was 71 and 11%, respectively. A high rate of toxicity was found

when compared with the 44% (all toxicity), the 21% (severe neutropenia) and 1% (FN) reported in a V-308 trial including younger patients (median age was 65 years; range 40-75) (20). On the other hand, non-hematological toxicity was similar to that found in a previous report and was deemed acceptable. Additionally, findings of our analysis revealed a correlation between the presence of grade 3 and 4 neutropenia for second-line FOLFIRI and the presence of severe neutropenia in first-line FOLFOX4. This suggests that the toxicity of previous treatment is a prognostic factor of tolerability with elderly patients to second-line FOLFIRI. Baseline characteristics such as female gender, the presence of comorbidity, and PS are normally associated with increased toxicity (21,22). We did not find such a correlation in this analysis. However, it is crucial to note that the power of this report, due to the low number of unhealthy patients, may be insufficient to detect such a correlation. In other words, even healthy elderly patients experienced severe neutropenia at a very high rate.

To avoid such a high rate of toxicity in a second-line setting following FOLFOX failure, single-agent irinotecan may be an appropriate approach in particular for elderly patients who experience severe neutropenia in first-line treatment. Single-agent irinotecan following fluoropyrimidine and oxaliplatin failure has been reported to be efficacious in mCRC patients, including the elderly (23). The outcome, with an overall response rate (RR) of 4.2% and a median PFS of 2.6 months was similar to our results. In elderly patients treated with fluoropyrimidine-based chemotherapy, single-agent irinotecan has proven to be safe in second-line therapy (severe neutropenia 22/35% for patients <70/≥70 years) (24).

The use of biological agents has not been well studied, even in healthy elderly patients. Cetuximab and irinotecan were found to improve PFS and RR in patients with wild-type KRAS in second-line treatment after fluoropyrimidine and oxaliplatin failure (23). A single retrospective study examined efficacy and safety of cetuximab with irinotecan in elderly patients with mCRC (25). Neutropenia and diarrhea were more frequent with cetuximab and irinotecan than irinotecan as a monotherapy. Therefore, more data are needed regarding toxicity in the elderly upon the addition of cetuximab.

Previous studies have focused on the UGT1A1 polymorphism as a determinant of irinotecan toxicity (26-28). It has been found that patients either heterozygous or homozygous for UGT1A1*28, a variant sequence in the promoter region, experienced more severe toxicity to irinotecan (29). However, to ascertain whether a reduced dose of irinotecan based on UGT1A1 polymorphism is appropriate requires prospective evaluation. It has been suggested that UGT1A7*3 is a marker for severe hematologic toxicity following the first cycle and that haplotype 1 is a predictor of severe hematologic toxicity during the entire course of therapy (30). The issue may be significant in treatment decision-making, particulary for elderly patients in second-line treatment due to the high rate of hematologic toxicity.

In conclusion, the use of all three active drugs in mCRC produces the longest OS in elderly patients as well as younger ones. However, second-line FOLFIRI may be toxic due to the high rate of severe hematological toxicity in the elderly. Further investigation is warranted in the second-line setting with elderly patients. This investigation should include the use of biological agents and the UGT1A polymorphisms. However, our data should be extrapolated to the majority of elderly patients undergoing second-line FOLFIRI with caution, even when in good health. In addition, we suggest that further investigation is needed involving more frail elderly patient cohorts.

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