Editorial Commentary

Lower incidence of adverse events about capecitabine and oxaliplatin from the GOIM 2802 study: a commentary

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The GOIM 2802 study is a randomized phase II trial to estimate the efficacy of bi-weekly XELOX (capecitabine plus oxaliplatin) with bevacizumab compared with FOLFOX4 [a bi-weekly bolus and infusional fluorouracil (FU) with folinic acid (FA) plus oxaliplatin] with bevacizumab in first-line therapy for patients with metastatic colorectal cancer (1). Generally, FOLFOX4 is a conventional treatment regimen for metastatic colorectal cancer (2). However, the continuous administration of FU requires the insertion of central venous catheters and infusion pumps, which inconvenient for patients and increases the risk of infections and thromboembolism.

Capecitabine, an oral fluoropyrimidine, has been known to be a convenient and well-tolerated agent with equal efficacy to infusional FU with FA (3). The efficacy of XELOX with or without bevacizumab had been demonstrated in several phase III trials for the first-line setting of metastatic colorectal cancer (4-6). Updated survival data from the NO16966 phase III trial showed that survival benefit was similar between XELOX and FOLFOX4 (7). Considering the result of pivotal phase III trials, the standard dose of XELOX regimen consists of a 2-hour infusion of oxaliplatin 130 mg/m^2 on day 1 plus oral capecitabine starting dose of 1,000 mg/m^2 twice daily for 2 weeks, repeated every 3 weeks. Until now, this tri-weekly XELOX regimen has been described in various regional guidelines as one of the treatment options in the first-line setting and frequently used for adjuvant chemotherapy, especially for stage III colorectal cancer (8-10).

In terms of effectiveness for the first-line setting, although the efficacy of tri-weekly XELOX and infusional FU plus oxaliplatin (e.g., FOLFOX4 and FUOX) are almost similar, the profile of adverse events are different (6,11). Based on NO16966 study which showed that XELOX with or without bevacizumab is non-inferior to FOLFOX with or without bevacizumab in the first-line treatment for mCRC, tri-weekly XELOX demonstrated more grade 3 hand-foot syndrome (6% *vs.* 1%) and diarrhea (19% *vs.* 11%) than FOLFOX4. In contrast, FOLFOX4 was associated with more grade 3 or 4 neutropenia (44% *vs.* 7%), and febrile neutropenia (6.3% *vs.* 3.8%) than tri-weekly XELOX (6).

Hand-foot syndrome, known as palmar-plantar erythrodysesthesia syndrome, acral erythema, and more recently grouped with the so-called toxic erythema of chemotherapy syndromes, is a relatively common skin reaction to fluoropyrimidine (e.g., capecitabine, FU, and S-1), pegylated liposomal doxorubicin and docetaxel (12). In particular, capecitabine is known to induce severe hand-foot syndrome, i.e., all grade hand-foot syndrome was occurred in 50–60% (grade 3 was approximately 25%) of patients treated with capecitabine alone (recommended dosage: 1,250 mg/m^2 twice daily) (12). Hand-foot syndrome is rarely life-threatening but can considerably decrease the quality of life of the patient, causing the need for a dose reduction or interruption of therapy, consequently limiting the use of a potentially effective therapy (13). Several prophylactic treatments, e.g., urea-based cream, COX2 inhibitor celecoxib, and pyridoxine (vitamin B6), are used

to preventing hand-foot syndrome but have a lack of useful robust data (14). Therefore, the most effective strategy to reduce hand-foot syndrome is considered dose modification or treatment interruption. Indeed, for example, patients treated with a reduced dose of capecitabine by adverse events presented almost the same efficacy compared with patients given the scheduled dose (15). Considering this unexpected efficacy of reduced capecitabine dose, searching a balance between efficacy and toxic profile, several doses and treatment schedules for capecitabine have been tested.

A randomized phase II trial, XELOX-A-DVS, which verify whether a dose-dense biweekly XELOX (capecitabine 1,500 mg/m^2 twice daily for 1 week) plus bevacizumab was superior to a standard tri-weekly XELOX regimen plus bevacizumab in the first-line treatment of patients with metastatic colorectal cancer or not, demonstrated a result that the dose-dense bi-weekly XELOX group showed a shorter median time to treatment failure and higher incidences of diarrhea and hand-foot syndrome than the standard tri-weekly XELOX (16). In the XELOX-A-DVS study, about half of patients (49%) in the dose-dense bi-weekly XELOX discontinued the study treatment by one or more intolerable adverse events. Based on these results, the authors didn't recommend the use of dose-dense bi-weekly XELOX.

Meiello *et al*. conducted a phase II trial of bi-weekly XELOX plus bevacizumab administration with a lower capecitabine dose (1,000 mg/m^2 twice daily for 1 week) compared to the standard tri-weekly XELOX (1,000 mg/m^2 twice daily for 2 weeks) (1). The given dose of capecitabine in this trial was 42,000 mg/m^2 for 6 weeks, which is a 75% dose of the conventional tri-weekly XELOX (56,000 mg/m^2 for 6 weeks).

Until now, including this GOIM2802 trial, a series of four phase II trials had investigated to explore the balance of efficacy and safety of bi-weekly XELOX regimen with or without bevacizumab in the first-line treatment of patients with metastatic colorectal cancer (1,17-19) (*Table 1*). In the series of four trials, the given dose of capecitabine was 1,000 mg/m^2 twice daily for 1 week, which set a lower cumulative dose than it of the standard tri-weekly XELOX. The incidence of any grade (grade 3) hand-foot syndrome of bi-weekly XELOX regimens in the four phase II trials varies between 12% and 42% (0 and 2%), and the incidence of diarrhea varies between 25.5% and 40% (0 and 7%) (1,17-19), while of the tri-weekly XELOX in the pivotal phase III trials, the incidence of any grade (grade 3) hand-foot syndrome varies between 20% and 40% (3% and 12%), and the incidence of diarrhea varies between 61% and 66% (14% and 22%) (4,7,11).

Concerning the salvage-line, a randomized phase II trial, ORION study, which had been planned as a third- or later-line therapy for 46 patients in whom reintroduction of oxaliplatin, compared the bi-weekly XELOX (capecitabine, 1,000 mg/m^2 twice daily for 1 week; oxaliplatin 85 mg/m^2 for 2 weeks) plus bevacizumab with the tri-weekly XELOX plus bevacizumab (20). There were no significant differences in efficacy, but the safety profile tended to be in favor of the bi-weekly schedule than the tri-weekly schedule with grade 3 or 4 diarrhea (0% in the bi-weekly regimen versus 9.1% in the tri-weekly regimen). Based on an indirect comparison of those data (20), the incidence of the hand-foot syndrome and diarrhea of the bi-weekly XELOX regimens showed lower than it of the standard tri-weekly schedule. Thus, the dose modification of capecitabine for bi-weekly schedule may increase the quality of life during treatment and prevent dose reduction or interruption of therapy.

In worldwide, for the first-line treatment of metastatic colorectal cancer, the oxaliplatin-based regimens are frequently used. Despite oxaliplatin is highly effective in combination with FU, oxaliplatin is often discontinued by hypersensitivity reaction or a cumulative sensory neuropathy that occurs at clinically significant levels by the threshold dose as over 550 mg/m^2 (21). Decreased dose intensity of oxaliplatin is considered to reduce neurotoxicity. The GOIM and GOIM2802 study out of the four bi-weekly XELOX trails used oxaliplatin at the dose of 100 mg/m^2 for 2 weeks, while the rest used 85 mg/m^2 for 2 weeks (1,19). The given dose of 85 mg/m^2 for 2 weeks in bi-weekly XELOX regimens is equal to the dose of standard FOLFOX regimens and almost equal to the dose of 130 mg/m^2 for 3 weeks in the standard tri-weekly XELOX regimen. In contrast, the dose of 100 mg/m^2 for 2 weeks used in the bi-weekly XELOX regimen estimates the higher cumulative dose than the other oxaliplatin-based regimens. Despite the higher dose density of oxaliplatin in the bi-weekly XELOX regimen in the GOIM and GOIM2802 study, the incidence of all grade peripheral sensory neuropathy was 18% and grade 3 was counted only one patient (1%) (1,19). With peripheral sensory neuropathy, of the four phase II trials (1,17-19), only the PHOENix study is associated with a high incidence of peripheral sensory neuropathy (all grade: 80.4%, grade 3: 14.3%), but the other three trials showed the incidence of grade 3 peripheral sensory neuropathy varied between 0 and 3% (*Table 1*) (17). Thus, as the incidence rate of peripheral sensory neuropathy

Table 1 Comparison of four phase II studies

Study	GOIM (19)	Grande *et al.* (18)	PHOENiX (17)	GOIM2802 (1)
Publication year	2009	2013	2016	2020
Number	59	35	51	87
Bevacizumab (mg/kg)	0	0	5	5
Oxaliplatin (mg/m^2)	100	85	85	100
Capecitabine (mg/m^2)	2,000	2,000	2,000	2,000
Age (median)	66	78	66	66
Objective response rate (%)	51	49	51	48.3
Disease control rate (%)	76	86	92.1	92
Median progression-free survival (months)	–	8.6	11.5	9.9
Median overall survival (months)	–	15.5	NR	25.0
Adverse event (%) [All grade (≥ grade 3)]				
Leucopenia	–	–	21.6 (7.8)	8 (0)
Neutropenia	17 (0)	14 (3)	21.6 (13.7)	16 (3)
Anemia	44 (0)	9 (0)	54.9 (0)	37 (3)
Thrombocytopenia	62 (6)	17 (0)	37.3 (0)	30 (2)
Stomatitis	–	11 (0)	35.3 (2)	17 (5)
Diarrhea	26 (2)	43 (3)	25.5 (0)	40 (7)
Hand-foot syndrome	–	20 (0)	49 (5.9)	12 (2)
Neuropathy	62 (0)	12 (3)	80.4 (13.7)	18 (1)

for those bi-weekly XELOX regimens tend to be equal or lower it for the conventional tri-weekly XELOX regimen (all grade is approximately 80% and grade 3 is approximately 15%) apparently, bi-weekly schedules of oxaliplatin (85–100 mg/m^2 for 2 weeks) might not be considered to increase the incidence of peripheral sensory neuropathy.

The GOIM2802 study design was non-comparative, but an exploratory comparison between FOLFOX4 plus bevacizumab, used as a calibration arm, and experimental arm (the bi-weekly XELOX plus bevacizumab) was performed (1). This GOIM2802 study met the primary endpoint with the objective response rate of the calibration group as 55.6% and it of the experimental group as 48.3% (P=0.43). Progression-free survival in the calibration arm and the experimental arm was 10.0 versus 9.9 months (P=0.84) and overall survival was 29.8 versus 25.0 months (P=0.41), respectively. This exploratory analysis showed that the bi-weekly XELOX plus bevacizumab has a comparable outcome with FOLFOX4 plus bevacizumab. Similar to this trial, the PHOENiX Japanese phase II trial enrolled untreated metastatic colorectal cancer patients to receive bi-weekly XELOX plus bevacizumab and reported an objective response rate of 51% with a median progression-free survival of 11.3 months (17). Although there may be a difference in the characteristics of enrolled patients (e.g., RAS mutation status) between PHOENiX and GOIM2802, the tumor effect is similar. As previously mentioned, the given dose of capecitabine in bi-weekly schedule was 14,000 mg/m^2 for 2 weeks, which is a 75% dose of the conventional triweekly schedule regimen (28,000 mg/m^2 for 3 weeks). What is worrisome about the dose reduction of capecitabine is the decrease in the anti-tumor effect. However, according to NO16966, the objective response rate and median progression-free survival with the tri-weekly XELOX plus bevacizumab patients (n=350) was 47% and 9.3 months (6). A direct comparison of objective response rate and median progression-free survival between the tri-weekly and the

bi-weekly XELOX is difficult, but there seems to be no significant difference in outcome between the two XELOX schedules in the first-line treatment of patients with metastatic colorectal cancer.

Compared with the conventional tri-weekly XELOX, although bi-weekly XELOX regimens have a disadvantage of increasing hospital visits, it may have an advantage of the lower incidence of adverse events (e.g., hand-foot syndrome and diarrhea) and be well tolerated. The bi-weekly XELOX plus bevacizumab might be one of the better options for the first-line treatment of patients with metastatic colorectal cancer, especially to avoid discontinuation of the scheduled treatment by severe subjective complications due to capecitabine overdose. Further large comparative clinical trials will be required to confirm these findings.

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