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ORIGINAL RESEARCH

5-Fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) plus sunitinib or bevacizumab as first-line treatment for metastatic colorectal cancer: a randomized Phase IIb study

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J Randolph Hecht[1]
Edith P Mitchell[2]
Takayuki Yoshino[3]
Manfred Welslau[4]
Xun Lin[5]
Edna Chow Maneval[6]
Jolanda Paolini[7]
Maria Jose Lechuga[7]
Albrecht Kretzschmar[8]

[1]David Geffen School of Medicine at UCLA, Santa Monica, CA, [2]Kimmel Cancer Center of Thomas Jefferson University, Philadelphia, PA, USA; [3]National Cancer Center Hospital East, Chiba, Japan; [4]Onkologische Praxis Klausmann/Welslau, Aschaffenburg, Germany; [5]Pfizer Oncology, La Jolla, [6]Seragon Pharmaceuticals, San Diego, CA, USA; [7]Pfizer Oncology, Milan, Italy; [8]Klinikum St Georg, Leipzig, Germany

Background: Sunitinib is an oral inhibitor of tyrosine kinase receptors implicated in tumor proliferation, angiogenesis, and metastasis. In this randomized, multicenter, open-label Phase IIb study, sunitinib plus mFOLFOX6 (oxaliplatin plus leucovorin plus 5-fluorouracil) was compared with bevacizumab plus mFOLFOX6 as first-line therapy in patients with metastatic colorectal cancer.

Methods: Patients were stratified by performance status, baseline lactate dehydrogenase level, and prior adjuvant treatment, and randomized 1:1 to receive sunitinib 37.5 mg/day for 4 weeks on and 2 weeks off plus mFOLFOX6 every 2 weeks or bevacizumab 5 mg/kg every 2 weeks plus mFOLFOX6 every 2 weeks. The primary endpoint was progression-free survival. Secondary endpoints included objective response rate, overall survival, safety, and quality of life.

Results: Enrollment was closed early following accrual of 191 patients, based on an interim analysis showing an inferior trend in the primary progression-free survival efficacy endpoint for sunitinib. Ninety-six patients were randomized to sunitinib plus mFOLFOX6 and 95 to bevacizumab plus mFOLFOX6. Median progression-free survival was 9.3 months and 15.4 months, respectively, but the objective response rate was similar between the study arms. Median overall survival was 23.7 months and 34.1 months, respectively. Dose reductions and interruptions were more common with sunitinib. Hematologic toxicity was more common in the sunitinib arm.

Conclusion: While the results of the sunitinib arm are comparable with those of previously reported FOLFOX combinations, the sunitinib-based combination was associated with more toxicity than that observed with bevacizumab and mFOLFOX6. The bevacizumab arm had an unexpectedly good outcome, and was much better than that seen in the Phase III trials. Combination therapy with sunitinib plus mFOLFOX6 is not recommended for patients with metastatic colorectal cancer.

Keywords: antiangiogenesis, bevacizumab, combination therapy, metastatic colorectal cancer, oxaliplatin, sunitinib

Introduction

Inhibition of angiogenic pathways has improved outcomes in a number of common malignancies. The addition of bevacizumab to fluoropyrimidine-based chemotherapy has been shown to increase response rates and prolong progression-free and overall survival rates when compared with chemotherapy alone in patients with metastatic colorectal cancer (mCRC).[1–3] This treatment strategy demonstrates the benefits of targeting vascular endothelial growth factor (VEGF) signaling in mCRC, but further

Correspondence: J Randolph Hecht
UCLA Department of Medicine, Division of Hematology-Oncology, 2825 Santa Monica Blvd #221, Santa Monica, CA 90404, USA
Tel +1 310 829 5471
Fax +1 310 586 0841
Email jrhecht@mednet.ucla.edu

improvements in clinical outcomes are needed, together with a greater understanding of other angiogenic pathways that may be involved in cancer proliferation and metastasis.

Sunitinib, an oral tyrosine kinase inhibitor, targets multiple angiogenic signaling pathways, including VEGF and platelet-derived growth factor receptors,[4–6] which may translate into increased antitumor activity when compared with single-target agents. In a Phase II study of single-agent sunitinib in 84 patients with chemorefractory mCRC, one partial response was observed in a patient previously treated with bevacizumab, and stable disease for ≥6 months was reported in two patients previously treated with bevacizumab and eleven patients who were bevacizumab-naïve.[7]

A Phase I dose-escalation study evaluating sunitinib for the first-line treatment of mCRC showed that the maximum tolerated dose was 37.5 mg/day on schedule 4/2 (4 weeks on, 2 weeks off) when used in combination with standard doses of irinotecan, leucovorin, and 5-fluorouracil. Common adverse events included neutropenia, diarrhea, and nausea. The combination showed evidence of antitumor activity, with eleven of 19 (58%) patients at the maximum tolerated dose achieving an objective response.[8] This randomized, multicenter, open-label, Phase IIb study (ClinicalTrials.gov identifier NCT00609622) compared a regimen of sunitinib plus 5-fluorouracil, leucovorin, and oxaliplatin (modified [m]FOLFOX6) with bevacizumab plus mFOLFOX6 for the first-line treatment of mCRC.

Materials and methods

Patients

Patients eligible for inclusion were at least 18 years of age, and had: histologically or cytologically confirmed adenocarcinoma of the colon or rectum with documented metastatic disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; evidence of measurable disease according to Response Evaluation Criteria in Solid Tumors;[9] and resolution of all acute toxic effects of prior therapy (except for alopecia) or surgical procedure to grade ≤1. Prior adjuvant therapy was permitted if more than 6 months had elapsed from completion of therapy and diagnosis of metastatic disease. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guidelines on Good Clinical Practice, and applicable local regulatory requirements and laws. Written informed consent was obtained from all patients.

Study design

Patients were randomized 1:1 to receive mFOLFOX6 (oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2 [or *l*-leucovorin 200 mg/m^2] as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m^2 as a bolus and 2,400 mg/m^2 as a 46-hour infusion) every 2 weeks, combined with either oral sunitinib at a starting dose of 37.5 mg/day for 4 weeks on treatment, followed by 2 weeks off treatment (schedule 4/2), or bevacizumab 5 mg/kg every 2 weeks. Prior to starting new cycles of treatment, hematologic parameters had to have recovered to grade ≤1. Treatment was continued until unacceptable toxicity or disease progression. Dose reductions or delays of sunitinib, bevacizumab, or mFOLFOX6 components were permitted to manage treatment-related toxicities. Sunitinib doses could be increased to 50 mg/day or reduced to 25 mg/day or 12.5 mg/day based on tolerability. Crossover between treatment arms was not permitted. Patients remained on study until disease progression or unacceptable toxicity. However, they were allowed to continue the treatment they had been randomized to if the investigator judged that there was evidence of clinical benefit. Patients who discontinued oxaliplatin due to oxaliplatin-related toxicity continued therapy with 5-fluorouracil/leucovorin plus sunitinib or bevacizumab. Those who discontinued treatment with all chemotherapy prior to disease progression continued treatment with sunitinib or bevacizumab as assigned at randomization (those receiving sunitinib were permitted to escalate the dose to 50 mg daily on schedule 4/2 at the investigator's discretion). Patients who discontinued all treatment prior to disease progression were followed for disease progression until initiation of a subsequent anticancer therapy in the absence of documented disease progression or until death, whichever occurred first. Patients were followed for at least 28 days after the last dose of study drug for adverse events, and were followed for overall survival until the study was terminated in May 2011.

Study objectives

The primary objective was to compare the efficacy of sunitinib and mFOLFOX6 with bevacizumab and mFOLFOX6 in terms of progression-free survival. Secondary objectives included measures of objective response rate, overall survival, safety, and tolerability, including patient-reported outcomes.

Study assessments

Tumor assessments were performed every 8 weeks. Efficacy evaluation was based on investigator's assessment using Response Evaluation Criteria in Solid Tumors 1.0 criteria. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0, and patient-reported outcomes on the Functional Assessment of Cancer Treatment-Colorectal (FACT-C)[10] and

the Functional Assessment of Cancer Treatment-Gynecologic Oncology Group Oxaliplatin-Specific Neurotoxicity (FACT&GOG-Ntx).[11] The FACT-C measures health-related quality of life in colorectal cancer patients on five subscales, ie, physical well-being, functional well-being, social/family well-being, emotional well-being, and the colorectal cancer subscale (which addresses concerns such as diarrhea). The FACT&GOG-Ntx is a treatment-specific subscale for neurotoxicity related to systemic chemotherapy.

Statistical analysis

The sample size for the primary efficacy endpoint of progression-free survival was determined based on the assumptions that the median progression-free survival for patients receiving bevacizumab plus mFOLFOX6 as first-line treatment was 10 months and that a 40% improvement in median progression-free survival (14 months) in the sunitinib arm was clinically significant. A total of 234 progression-free survival events were required for a one-sided stratified log-rank test with a significance level of 0.05 and power of 80% to detect a statistically significant difference between treatment arms. Assuming accrual was accomplished over a 12-month period and follow-up was continued for at least 24 months after the last patient was enrolled, a total sample size of approximately 290 patients (145 patients per treatment arm) was required. This sample size also allowed for assessment of differences in the secondary endpoint of overall survival. With an expected median overall survival of 20 months in the comparator arm, a total of 223 deaths were required to observe a difference in median overall survival from 20 months (bevacizumab arm) to 28 months (sunitinib arm) using a one-sided, stratified log-rank test with an overall significance level of 0.05 and power of 80%. The planned follow-up duration for overall survival was 47 months.

Analyses were performed for all patients who were enrolled into the study (efficacy analyses) and who received at least one dose of study medication (safety analyses). Descriptive statistics were used to summarize patient characteristics, safety, and patient-reported outcomes. Kaplan–Meier methods were used to estimate median progression-free survival and overall survival, and stratified log-rank tests (one-sided, α=0.05) were used to detect statistically significant differences between the two treatment arms with 80% power. Progression-free survival was derived based on tumor assessments by the investigators. Patients were stratified by ECOG performance status (0 versus 1), prior adjuvant therapy (yes versus no), and baseline lactate dehydrogenase (LDH) levels (high, defined as $>1.5\times$ the upper limit of normal versus low, defined as $\leq 1.5\times$ the upper limit of normal). Serum LDH was selected for analysis because high levels are correlated with poor prognosis in colorectal cancer[12] and predict significantly shorter progression-free survival and overall survival in patients receiving chemotherapy alone.[13] However, a high LDH level appears to predict a somewhat better response to antiangiogenic agents in combination with chemotherapy,[13–15] consistent with its role as a potential marker of hypoxia. No biomarkers other than LDH were analyzed.

An interim analysis of progression-free survival was planned when approximately 50% of the total progression-free survival events had been observed, as determined by investigator assessments confirmed by independent central review.

Results

Baseline characteristics and patient disposition

The study was conducted at 76 centers in the USA, Germany, Japan, and Denmark between April 2008 and July 2011. Planned study enrollment was 290 patients; however, enrollment closed early with 191 patients randomized. A planned interim analysis of efficacy data showed an inferior trend that was unlikely to demonstrate a statistically significant improvement in the primary progression-free survival endpoint for sunitinib as compared with bevacizumab. Efficacy data continued to mature until the study was terminated in May 2011.

The 191 randomized patients constituted the full analysis population; 96 were randomized to sunitinib plus mFOLFOX6 and 95 were randomized to bevacizumab plus mFOLFOX6. Baseline patient and disease characteristics are summarized in Table 1. The treatment arms were comparable in terms of age, performance status, prior adjuvant therapy, and levels of LDH and carcinoembryonic antigen. There were slightly more Asians in the sunitinib arm than in the bevacizumab arm (21.9% versus 12.6%). Most patients (129; 67.5%) had an ECOG performance status of 0 at study entry (Table 1).

Patient disposition is shown in Figure 1. The majority of patients withdrew from the study due to objective progression or relapse (46.1%), adverse events (12.6%), or refusal of treatment for reasons other than adverse events (12.6%). Nineteen patients (9.9%) withdrew specifically because of study termination (16.7% in the sunitinib arm and 3.2% in the bevacizumab arm).

Efficacy

Progression-free survival

The primary endpoint of the study was not met: sunitinib and mFOLFOX6 failed to demonstrate superior progression-free

Table 1 Demographic and baseline characteristics

	Sunitinib + mFOLFOX6 (n=96)	Bevacizumab + mFOLFOX6 (n=95)
Median age (range), years	61 (34–83)	60 (32–80)
Sex, n (%)		
Male	61 (64)	62 (65)
Female	35 (37)	33 (35)
Race, n (%)		
White	63 (66)	69 (73)
Black	7 (7)	9 (10)
Asian	21 (22)	12 (13)
Other	5 (5)	5 (5)
Median CEA level (range), ng/mL	29.60 (0.8–4,741.4)	35.90 (0.8–6,064.2)
ECOG PS, n (%)		
0	65 (68)	64 (67)
1	31 (32)	31 (33)
Prior adjuvant therapy, n (%)		
No	85 (89)	86 (91)
Yes	11 (12)	9 (10)

Abbreviations: CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status.

survival compared with bevacizumab and mFOLFOX6. Median progression-free survival in the sunitinib and mFOLFOX6 arm was 9.3 months (95% confidence interval [CI] 9.2–11.1 months) compared with 15.4 months (95% CI not available because data were not mature) in the bevacizumab and mFOLFOX6 arm (Figure 2). The hazard ratio comparing the sunitinib and bevacizumab arms was 2.366 (95% CI 1.152–4.863), with a one-sided stratified log-rank *P*-value of 0.9920.

Baseline LDH did not have a significant impact on progression-free survival in either treatment arm. Among patients receiving sunitinib, median progression-free survival was 9.2 months in those with high baseline LDH and 9.4 months in those with low baseline LDH. Among those receiving bevacizumab, median progression-free survival was not reached in patients with high baseline LDH, and was 15.4 months in those with low baseline LDH.

Secondary endpoints

The objective response rate was 42.9% (95% CI 32.5–53.7) for the sunitinib arm and 40.0% (95% CI 29.8–50.9) for the bevacizumab arm. This difference was not statistically significant (95% CI −11.5 to 17.2; *P*=0.6964). The rates of complete response, partial response, stable disease, and progressive disease are shown in Table 2. The maximum percentage change in target lesion size for each patient is shown in Figure 3. Forty-seven (49.0%) patients died in the sunitinib arm versus 34 patients (35.8%) in the bevacizumab arm. Median overall survival was 23.7 months (95% CI 19.4, not reached) and 34.1 months (95% CI 23.3–34.2), respectively (hazard ratio 1.477, 95% CI 0.910–2.301; *P*=0.9418).

Treatment exposure

The overall median duration of study drug treatment was shorter for sunitinib than for bevacizumab (6.2 months versus

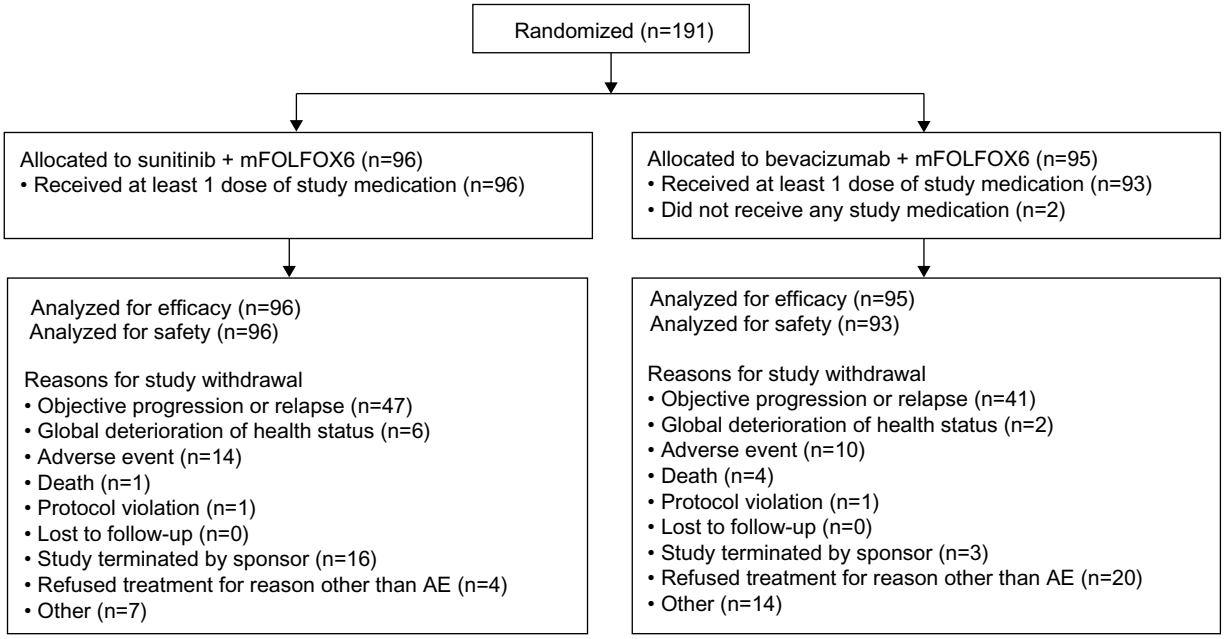

Figure 1 CONSORT diagram.
Abbreviation: AE, adverse event.

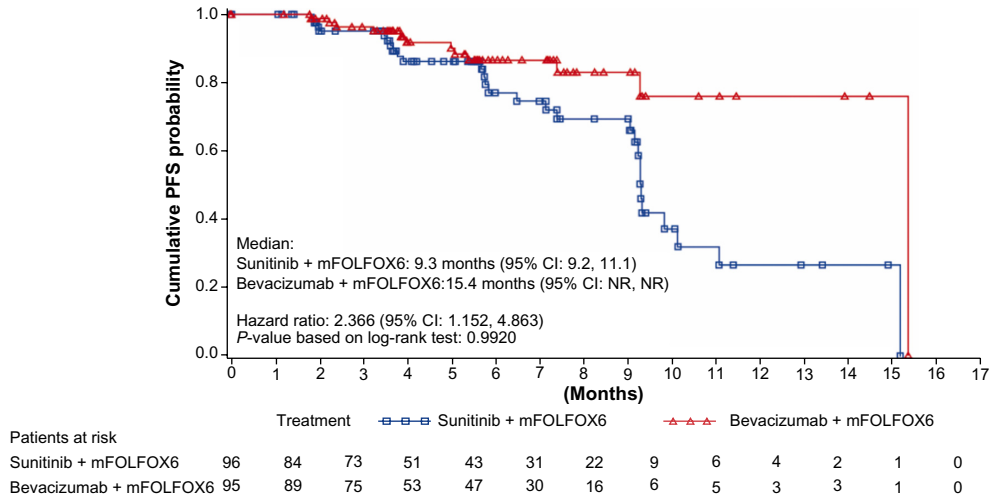

Figure 2 Kaplan–Meier estimates of progression-free survival.
Abbreviations: CI, confidence interval; PFS, progression-free survival; NR, not reached.

7.1 months, respectively). Patients started fewer cycles of sunitinib than bevacizumab (median 10.5 versus 14.0 cycles, respectively). More patients had dose reductions in the sunitinib arm than in the bevacizumab arm (41.7% versus 14.0%, respectively). Likewise, more patients had dose interruptions in the sunitinib arm than in the bevacizumab arm (45.8% versus 7.5%, respectively). However, cycle delays were less frequent in the sunitinib arm than in the bevacizumab arm (44.8% versus 73.1%, respectively). Adverse events were the most common reason for dose reductions, dose interruptions, and cycle delays.

These findings are reflected in a lower relative dose intensity in the sunitinib arm than in the bevacizumab arm (median 80.3% versus 96.3%, respectively). Similarly, relative dose intensity for oxaliplatin and 5-fluorouracil bolus/infusion was lower in the sunitinib arm than in the bevacizumab arm.

Safety

Safety was analyzed for all patients who received at least one dose of study medication (n=96 for sunitinib and n=93 for bevacizumab). The most common adverse events in the sunitinib arm were neutropenia, diarrhea, and fatigue, while the most common adverse events in the bevacizumab arm were fatigue, nausea, and diarrhea (Table 3). Most adverse events were grade 1 or 2. The most common grade 3 and 4 adverse events occurring more frequently in the sunitinib arm than in the bevacizumab arm were neutropenia, thrombocytopenia, and fatigue.

Table 2 Best overall response in each treatment arm

	Sunitinib + mFOLFOX6 (n=96)	Bevacizumab + mFOLFOX6 (n=95)
Complete response, n (%)	1 (1.0)	1 (1.1)
Partial response, n (%)	38 (39.6)	35 (36.8)
Stable disease, n (%)	44 (45.8)	53 (55.8)
Progressive disease, n (%)	3 (3.1)	1 (1.1)

Serious adverse events were reported in 36 patients (37.4%) in the sunitinib arm and 30 patients (32.3%) in the bevacizumab arm. The serious adverse events were judged to be treatment-related in 18 patients (18.8%) and 15 patients (16.1%), respectively. The most common serious adverse events (occurring in at least three patients) not related to disease progression were febrile neutropenia, intestinal obstruction, and dehydration in the sunitinib arm, and deep vein thrombosis, which was only reported in the bevacizumab arm. Among the reported serious adverse events, eight patients (4.2%) died during treatment or within 28 days of the last dose of study drug; these included five deaths (5.2%) in the sunitinib arm (two due to progressive disease, one due to aspiration, one due to left ventricular systolic dysfunction, and one due to pulmonary hypertension) and three (3.2%) in the bevacizumab arm (all attributed to progressive disease).

Most adverse events and hematologic abnormalities were manageable with dose modifications or delays. The most common adverse events related to mFOLFOX6 plus either sunitinib or bevacizumab that caused dose modification were neutropenia and thrombocytopenia, and the most common adverse event related to sunitinib or bevacizumab that caused dose modification was diarrhea in both arms (but to a greater extent in the sunitinib arm). The most common

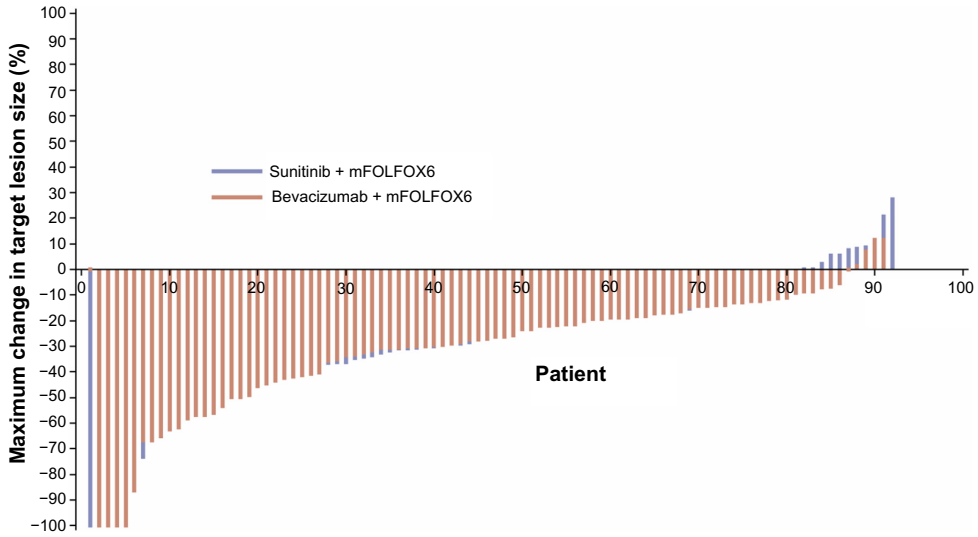

Figure 3 Maximum percentage change in target lesion size.

adverse event related to mFOLFOX6 that caused dose modification was peripheral neuropathy (to a greater extent in the bevacizumab arm).

Forty patients (41.7%) in the sunitinib arm and 39 patients (41.9%) in the bevacizumab arm discontinued treatment during the study as a result of adverse events. The most common adverse events leading to discontinuation in both arms were peripheral neuropathy, peripheral sensory neuropathy, and neutropenia.

Table 3 Treatment-emergent adverse events by MedDRA preferred term and maximum CTCAE grade, occurring in ≥30% of subjects (all causality, all cycles)

Preferred term	Sunitinib + mFOLFOX6 (n=96) n (%)		Bevacizumab + mFOLFOX6 (n=93) n (%)	
	All grades	Grade 3/4	All grades	Grade 3/4
Fatigue	65 (67.7)	13 (13.5)	62 (66.7)	9 (9.7)
Nausea	62 (64.6)	2 (2.1)	57 (61.3)	3 (3.2)
Diarrhea	66 (68.8)	9 (9.3)	49 (52.7)	7 (7.5)
Neutropenia	68 (70.8)	49 (51.0)	33 (35.5)	18 (19.4)
Peripheral neuropathy	39 (40.6)	6 (6.3)	37 (39.8)	6 (6.5)
Thrombocytopenia	50 (52.1)	23 (24.0)	19 (20.4)	3 (3.2)
Decreased appetite	32 (33.3)	1 (1.0)	36 (38.7)	1 (1.1)
Vomiting	34 (35.4)	6 (6.3)	34 (36.6)	3 (3.2)
Peripheral sensory neuropathy	29 (30.2)	10 (10.4)	33 (35.5)	7 (7.5)
Stomatitis	31 (32.3)	3 (3.1)	26 (28.0)	3 (3.2)
Anemia	27 (28.1)	5 (5.2)	26 (28.0)	5 (5.4)
Constipation	22 (22.9)	1 (1.0)	31 (33.3)	1 (1.1)
Epistaxis	23 (24.0)	1 (1.0)	30 (32.3)	0 (0.0)
Dysgeusia	31 (32.3)	0 (0.0)	21 (22.6)	0 (0.0)

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities.

Patient-reported outcomes

Responses on the FACT-C and FACT&GOG-Ntx were available for 93 and 90 patients at baseline and 78 and 82 patients through cycle 3, for sunitinib and bevacizumab, respectively. Mean baseline FACT-C scores were similar in both groups. No clinically meaningful or statistically significant differences were observed between treatments in either the FACT-C subscales or the FACT&GOG/Ntx neurotoxicity subscale from baseline to cycle 4 day 1. Functional well-being subscale scores worsened in the sunitinib group (mean −0.78 points) but improved in the bevacizumab group (mean 1.56 points). The mean difference between treatments was −2.34 points (95% CI −3.98 to −0.70; P=0.006). Differences greater than three points were considered clinically meaningful.[16]

Discussion

The combination of sunitinib 37.5 mg/day on schedule 4/2 and mFOLFOX6 was more toxic and less effective than bevacizumab 5 mg/kg every 2 weeks and mFOLFOX6. Overall toxicity, and hematologic toxicity in particular, was greater in the sunitinib arm. This is not surprising, as oxaliplatin-containing regimens such as mFOLFOX6 have long been known to cause neutropenia and thrombocytopenia,[17–19] and have been reported with the use of sunitinib as a single agent.[20] The combination of sunitinib with cytotoxic chemotherapy appears to produce an even greater incidence of cytopenias.[8,21,22]

Although overall response rates were equivalent, progression-free survival (as confirmed by independent third party review) and overall survival were much longer in the bevacizumab-containing arm. One possible explanation is

that the higher incidence of some adverse events in the sunitinib arm required more dose reductions, dose interruptions, and cycle delays, leading to a shorter overall median duration of treatment in the sunitinib arm. The shorter progression-free survival and overall survival observed in the sunitinib arm do not seem to be obviously related to toxicity, as the number of patients who discontinued due to toxicity was relatively low. Furthermore, the progression-free survival of 9.3 months and overall survival of 23.7 months in the sunitinib arm are comparable with those seen in other studies with similar regimens.[3,14] However, the progression-free survival of 15.4 months and overall survival of 34.1 months in the bevacizumab arm were much better than that reported previously with other bevacizumab-containing regimens in the first-line treatment of mCRC, including bevacizumab combined with capecitabine plus oxaliplatin (XELOX),[3] or with oxaliplatin and/or irinotecan-based chemotherapies (FOLFOX4, FOLFIRI, FOLFOXIRI).[3,23] Based on previous trials, the median progression-free survival was expected to be approximately 10 months, and this estimate was used for the sample size calculation in this study. It is possible that this was an exceptional group of patients and that sunitinib caused them to do worse than they would have done otherwise, but the measured baseline characteristics of the patients in the study were well balanced and did not differ significantly from those reported for larger trials in this indication. Other possible explanations are a deleterious impact of combined treatment with sunitinib and mFOLFOX6 or a negative interaction between sunitinib and chemotherapy. Indeed, in terms of tolerability, the schedule selected may have been suboptimal. The dose of sunitinib was selected based on the maximum tolerated dose in a Phase I study in combination with FOLFIRI.[8] However, at that time there were no data to support using this dose with FOLFOX regimens, which have more overlapping toxicities with sunitinib (eg, thrombocytopenia). Yoshino et al recently reported that sunitinib plus mFOLFOX6 had acceptable tolerability in treatment-naïve colorectal cancer, but that a 2-week on/2-week off schedule (schedule 2/2) was generally more manageable than schedule 4/2.[24] In a recent study of patients with advanced solid malignancies, including mCRC, the combination of sunitinib with mFOLFOX6 had acceptable tolerability. The most common adverse events were neutropenia, fatigue, and thrombocytopenia. The maximum tolerated doses were 50 mg/day on schedule 2/2 and 25 mg/day on a continuous daily dosing schedule. Schedule 4/2 was evaluated but the maximum tolerated dose was not established.[21]

A small molecule VEGF receptor tyrosine kinase inhibitor, regorafenib, was recently shown to improve progression-free survival and overall survival compared with best supportive care as a single agent in the salvage setting;[25] however, it has been difficult to show significant improvement in outcome by adding drugs of this class to standard cytotoxic therapy. Another VEGF receptor tyrosine kinase inhibitor, vatalanib, did not improve progression-free survival or overall survival when added to FOLFOX4 in the first-line or second-line setting.[14,15] Recently, the results of the HORIZON II and III trials showed that adding the VEGF receptor tyrosine kinase inhibitor, cediranib, to an oxaliplatin-containing regimen produced a modest benefit in progression-free survival but no improvement in overall survival,[26] and no benefit compared with adding bevacizumab.[27] A large randomized trial of adding sunitinib 37.5 mg/day on schedule 4/2 to FOLFIRI in first-line therapy was also negative, with no significant effect on progression-free survival but greater toxicity, more deaths as a result of toxicity, and significantly more dose delays, dose reductions, and treatment discontinuations in the sunitinib arm.[28] Bevacizumab, on the other hand, has been shown to improve both progression-free survival and overall survival in combination with older regimens when compared with chemotherapy alone.[1–3]

While inhibiting the same pathway, small molecule VEGF receptor tyrosine kinase inhibitors and bevacizumab differ from each other in their targets, pharmacokinetics, and toxicity profiles.[29] The development of robust predictive markers may help explain these differences. In conclusion, the combination of sunitinib with mFOLFOX6 was more toxic and less effective than bevacizumab and the same chemotherapy.

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