A Randomized, Open-Label, Multicenter, Phase 3 Study of High-Dose Vitamin C Plus FOLFOX ± Bevacizumab versus FOLFOX ± Bevacizumab in Unresectable Untreated Metastatic Colorectal Cancer (VITALITY Study)

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ABSTRACT

Purpose: To compare the efficacy and safety of high-dose vitamin C plus FOLFOX ± bevacizumab versus FOLFOX ± bevacizumab as first-line treatment in patients with metastatic colorectal cancer (mCRC).

Patients and Methods: Between 2017 and 2019, histologically confirmed patients with mCRC ($n = 442$) with normal glucose-6-phosphate dehydrogenase status and no prior treatment for metastatic disease were randomized (1:1) into a control (FOLFOX ± bevacizumab) and an experimental [high-dose vitamin C (1.5 g/kg/d, intravenously for 3 hours from D1 to D3) plus FOLFOX ± bevacizumab] group. Randomization was based on the primary tumor location and bevacizumab prescription.

Results: The progression-free survival (PFS) of the experimental group was not superior to the control group [median PFS, 8.6 vs. 8.3 months; HR, 0.86; 95% confidence interval (CI), 0.70–1.05; $P = 0.1$]. The objective response rate (ORR) and overall survival (OS) of the experimental and control groups were similar (ORR, 44.3% vs. 42.1%; $P = 0.9$; median OS, 20.7 vs. 19.7 months; $P = 0.7$). Grade 3 or higher treatment-related adverse events occurred in 33.5% and 30.3% of patients in the experimental and control groups, respectively. In prespecified subgroup analyses, patients with RAS mutation had significantly longer PFS (median PFS, 9.2 vs. 7.8 months; HR, 0.67; 95% CI, 0.50–0.91; $P = 0.01$) with vitamin C added to chemotherapy than with chemotherapy only.

Conclusions: High-dose vitamin C plus chemotherapy failed to show superior PFS compared with chemotherapy in patients with mCRC as first-line treatment but may be beneficial in patients with mCRC harboring RAS mutation.

Introduction

The use of vitamin C in cancer treatment can be traced to more than 40 years ago, when Cameron and Pauling (1, 2) published two retrospective studies reporting the survival prolongation of patients with advanced cancer after treatment with intravenous high-dose vitamin C. However, these findings could not be reproduced in two subsequent prospective controlled clinical studies using oral vitamin C (3); possibly due to the route of administration that strongly affects the pharmacokinetics of vitamin C (4). Complete plasma saturation usually occurs at a daily oral dose of ≥400 mg of vitamin C in humans, achieving a blood concentration of 60–100 μmol/L. In contrast, intravenous vitamin C can achieve a blood concentration of up to 20 mmol/L, which is more than 200 times greater than that observed orally (4, 5). *In vitro*, it has been observed that 0.3–30 mmol/L (also termed therapeutic concentration) of vitamin C could effectively kill a variety of cancer cells and had no significant impact on normal cells; *in vivo*, tumor growth was inhibited when mice were given vitamin C infusion whereas no significant tumor inhibition was observed under the same dose orally (6, 7). Therefore, to achieve therapeutic concentration and produce tumor inhibition effect, the intravenous administration of vitamin C is preferred (8).

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Translational Relevance

Our preclinical study identified synergistic antitumor effects between vitamin C and chemotherapy. Our follow-up phase I dose-escalation trial showed that intravenous high-dose vitamin C plus chemotherapy was well tolerated in patients with metastatic colorectal cancer (mCRC). Thus, we performed the first randomized, multicenter, phase 3 clinical trial to investigate whether intravenous high-dose vitamin C could potentiate the efficacy of FOLFOX ± bevacizumab in 442 chemotherapy-naïve patients with mCRC randomized into a vitamin C plus chemotherapy and chemotherapy-only group. The study did not meet the primary endpoint of progression-free survival (PFS), but in the prespecified subgroup analysis, patients with RAS mutation had improved PFS with vitamin C plus chemotherapy than those with chemotherapy only. The objective response rate, treatment-related adverse events, and overall survival were similar in the two groups. High-dose vitamin C failed to further prolong the PFS of patients with mCRC but may be beneficial in patients with RAS mutation.

Intravenous vitamin C alone or with chemotherapy has been shown to be safe in patients with advanced solid tumors (9). Two phase 1 dose-escalation trials conducted in patients with advanced cancer showed that high-dose intravenous vitamin C of up to 110 g/m^2 or 1.5 g/kg as monotherapy was safe and had no serious adverse event (10, 11). In preclinical studies, vitamin C showed synergetic effects with some chemotherapy and immunotherapy drugs under different modes of action (12–16). Findings from a phase 1/2 trial performed on ovarian cancer demonstrated a trend toward disease progression and overall survival (OS) improvements when vitamin C was combined with standard chemotherapy (17). Another phase 2 clinical study showed that low-dose vitamin C with decitabine was associated with longer OS than decitabine alone in elderly patients with acute myelogenous leukemia (18).

Yun and colleagues (19) found that high-dose vitamin C could selectively kill cultured human colorectal cancer cells harboring KRAS or BRAF mutations and inhibit colorectal tumor growth in Apc/Kras^{G12D}-mutant mice. Our group found a synergistic effect between high-dose vitamin C and oxaliplatin in tumor cell lines and animal models via an increase in oxidative stress (20). We have thus completed a phase 1 dose-escalation trial of intravenous vitamin C combined with chemotherapy, in which 7 doses were studied. Our findings showed favorable safety profiles and preliminary efficacies and provided the recommended dose for high-dose vitamin C in combination with chemotherapy (21). To date, no prospective phase 3 trials comparing the safety and efficacy of vitamin C combined with chemotherapy and chemotherapy-only have been reported. Thus, it is important to examine the anticancer effects of intravenous vitamin C on a specific tumor type in randomized controlled phase 3 settings. In the VITALITY study, we performed a randomized, multicenter, phase 3 clinical trial to compare the efficacy and safety of intravenous high-dose vitamin C plus FOLFOX ± bevacizumab versus FOLFOX ± bevacizumab as first-line treatment in patients with mCRC.

Patients and Methods

Patients

Patients were considered eligible if they were of ages between 18 and 75 years old, and had stage IV colorectal cancer with measurable disease lesions according to the RECIST version 1.1, an initial unresectable lesion and no prior treatment for metastatic disease. Other eligibility criteria included an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0 to 2, a normal glucose-6-phosphate dehydrogenase (G6PD) level and adequate organ function. Patients with previous adjuvant or neoadjuvant chemotherapy for colorectal cancer were also eligible if the earlier treatment had been completed at least 12 months before randomization. Patients were enrolled from 14 sites across China between July 2017 and December 2019.

Trial design and treatment

The patients were randomly allocated into a control group and an experimental group, in a 1:1 ratio, using the stratified block randomization method. Sequentially numbered opaque sealed envelopes were used to maintain allocation concealment. Seed numbers were specified using the stratified block randomization method, and the SAS statistical software was used to generate a randomized sequence. The two stratification factors for randomization were: (i) treatment with or without bevacizumab, and (ii) location of primary lesion (left/right). Right-sided colon carcinomas encompassed the cecum, ascending colon, and transverse colon. Left-sided colon carcinomas encompassed the splenic flexure, descending colon, sigmoid colon, and rectum. The randomized sequence was generated by a statistician. Enrollment was conducted by the study physicians, and written informed consents from the patients were obtained. Study nurses or clinical research coordinators were responsible for unsealing the envelopes for assignment results and recording the patients' treatment group.

The experimental group was treated with high-dose vitamin C (1.5 g/kg/d intravenously for 3 hours from day 1 to day 3) plus mFOLFOX6 with or without bevacizumab. The control group was treated with mFOLFOX6 with or without bevacizumab every two weeks intravenously. mFOLFOX6 was administered intravenously and consisted of oxaliplatin (85 mg/m^2 on day 1), leucovorin (400 mg/m^2 on day 1) and 5-fluorouracil (400 mg/m^2 on day 1, followed by 2,400 mg/m^2 over 46 to 48 hours continuous infusion) with or without bevacizumab (5 mg/kg intravenously on day 1).

Treatment was continued for a maximum of 12 cycles or until disease progression, unacceptable toxicities, or a decision by the physician or patient to withdraw from the trial. After 12 treatment cycles, investigators communicated with the patients to decide whether to continue the 5-fluorouracil or capecitabine with or without bevacizumab (only for patients with prior bevacizumab treatment) as maintenance treatment. Vitamin C was discontinued after 12 cycles. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics committee of Sun Yat-sen University Cancer Center (ID: B2017–014–01).

Assessment of response, survival, and adverse events

Tumor response was assessed according to the RECIST criteria, version 1.1, by the study investigators at 6 weeks from drugs administration and then every 6 weeks (±2 weeks) until progressive disease (PD). During follow-up, survival was assessed every 9 weeks. Treatment-related adverse events (TRAE) were evaluated throughout the trial and at 30 days (for patients with serious adverse events, till 90 days) after treatment discontinuation and were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.

Endpoints

The primary endpoint was progression-free survival (PFS; time from randomization to first disease progression, as assessed according to RECIST, version 1.1, or death from any cause). Secondary endpoints included OS, objective response rate (ORR; complete or partial response) as determined according to RECIST, version 1.1, and safety. Exploratory endpoints included the correlation of the RAS (KRAS, NRAS, and HRAS) pathway changes and the antitumor activity of high-dose vitamin C, the pharmacokinetic characteristics of intravenous high-dose vitamin C, the mechanism of high-dose vitamin C response, and acquired resistance by evaluating the predictive biomarkers/mutations in blood and tumor.

Statistical analyses

Efficacy was assessed in the intention-to-treat (ITT) population, which consisted of all patients who underwent randomization. Safety was assessed in the as-treated population, which included patients who underwent randomization and received at least one study treatment. The Kaplan–Meier method was used to estimate survival endpoints. In the analysis of PFS, data for patients who were alive without disease progression were censored as of the time of the last imaging assessment; data for patients who had surgery with curative intent were censored as of the date of surgery. Deaths that occurred without disease progression were included as events in the evaluation of PFS. For the analysis of OS, data for patients without documented death at data cutoff were censored as of the last known date the patients were alive. The log-rank test was used to assess between-group differences in both PFS and OS. Hazard ratio (HR) and associated 95% confidence interval (CI) were calculated using the Cox proportional-hazards model. The proportional-hazards assumption of PFS was examined by both graphical and analytic methods. PFS rate at 6 months (6-month PFS rate) was compared using the two-sample test for between-group differences described by Klein and colleagues (22) with log-transformed survival functions and unpooled variances. Differences in response rates were assessed with the χ^2 test. Subgroup analyses of the outcomes were carried out to assess for a treatment effect in terms of RAS and BRAF status (prespecified subgroups), gender, age, primary site, usage of bevacizumab, ECOG PS, and maintenance therapy. The Kaplan–Meier method was used to estimate the median PFS of each arm of these subgroups. For each subgroup, HRs and 95% CIs were calculated by Cox proportional-hazards model, and log-rank test was used to compare the differences between the two arms. All statistical analyses were performed using the R software (version 4.0.4).

According to reports in literature, the median PFS of the control group is 8 months. The estimated median PFS of the study group is

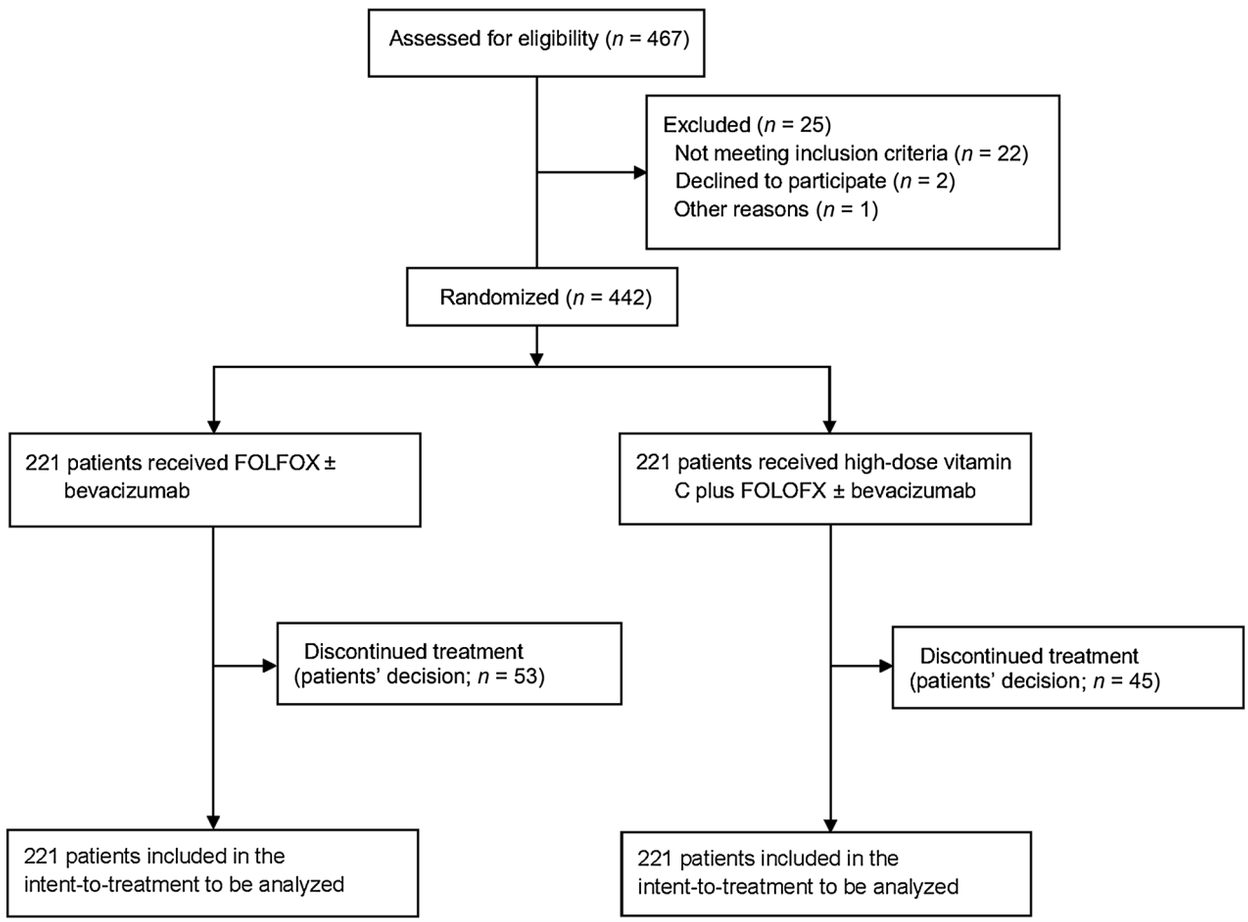

Figure 1.
Generalized profile of this study.

11 months (HR, 0.727). The study was designed for 80% power to detect improvement in PFS, using a one-sided log-rank test at the significance level of 0.025. The estimated enrollment period was 24 months, and the follow-up period was 12 months. Considering a 10% of patients lost during follow-up, a minimum of 216 patients for per group and a total of 432 patients for the study were required, as calculated with PASS version 15 (NCSS, LLC).

Data availability

Because of patients' privacy and related regulations in China, if a researcher wants to use our raw data for scientific research purposes, they can apply for use with our corresponding author and database administrator.

Results

Patient characteristics

Between July 2017 and December 2019, 442 patients were enrolled and randomly assigned to receive either high-dose vitamin C plus chemotherapy (experimental group) or chemotherapy-only (control group), in a 1:1 ratio (**Fig. 1**). The demographic characteristics, including sidedness of the primary tumor, use of bevacizumab and RAS/BRAF status, were well balanced between the two groups (**Table 1**; Supplementary Table S1). The median age of the entire cohort was 57 (range, 18 to 75) years. 319 patients (72.2%) had left-sided primary tumors, and 203 (45.9%) and 14 (3.2%) had RAS mutant and $BRAF^{V600E}$ mutant tumors, respectively (**Table 1**).

The cutoff date was December 30, 2020. It was more than 12 months since the last patient was enrolled. The median follow-up time of the study since randomization was 24.5 (range, 0.73–42.5) months. A total of 221 patients in each group received at least one dose of assigned treatment. The median duration of treatment exposure was 4.5 months in each group. A total of 139 patients (31.4%) received maintenance therapy, comprising of 70 (31.7%) patients from the experimental group and 69 (31.2%) from the control group.

PFS

The median PFS of the ITT population was 8.6 (95% CI, 7.7–10.0) months for patients treated with high-dose vitamin C plus chemotherapy and 8.3 (95% CI, 7.9–9.1) months for chemotherapy only. Overall, treatment with high-dose vitamin C demonstrated a tendency to prolong PFS. However, the prespecified statistical criteria for the superiority of high-dose vitamin C plus chemotherapy over chemotherapy were not met (HR, 0.86; 95% CI, 0.70–1.05; $P = 0.1$; **Fig. 2A**).

Prespecified subgroup analyses, based on RAS or BRAF status, showed that patients with RAS mutation had significantly improved PFS with high-dose vitamin C plus chemotherapy than with chemotherapy only (9.2 vs. 7.8 months; HR, 0.67; 95% CI, 0.50–0.91; $P = 0.01$; **Fig.2B**; Supplementary Fig. S1). For RAS mutant patients, sidedness, use of bevacizumab, treatment cycles, treatment duration, and maintenance therapy were well balanced between those with and without vitamin C (Supplementary Table S3). Multivariate analyses further showed that high-dose vitamin C added to chemotherapy was an independent factor for prolonging the PFS of RAS mutant patients

Table 1. Characteristics of patients at enrollment.

Characteristics, *N* (%)	All patients (*N* = 442)	Experimental group (*N* = 221)	Control group (*N* = 221)	*P*
Gender				
Female	171 (38.7)	88 (39.8)	83 (37.6)	0.7
Male	271 (61.3)	133 (60.2)	138 (62.4)	
Age (mean ± SD)	55.7 ± 11.2	55.4 ± 11.3	56.1 ± 11.0	0.5
Age				
<55	178 (40.3)	91 (41.2)	87 (39.4)	0.8
≥55	264 (59.7)	130 (58.8)	134 (60.6)	
Primary tumor site				
Left-sided	319 (72.2)	161 (72.9)	158 (71.5)	0.8
Right-sided	123 (27.8)	60 (27.1)	63 (28.5)	
Weight (mean ± SD)[a]	60.7 ± 11.4	60.0 ± 10.8	61.4 ± 11. 9	0.2
ECOG PS				
0	212 (48.0)	101 (45.7)	111 (50.2)	0.5
1	218 (49.3)	115 (52.0)	103 (46.6)	
2	12 (2.7)	5 (2.3)	7 (3.2)	
RAS				
Mutant	203 (45.9)	103 (46.6)	100 (45.2)	0.7
Unknown	40 (9.0)	22 (10.0)	18 (8.1)	
Wild-type	199 (45.0)	96 (43.4)	103 (46.6)	
$BRAF^{V600E}$				
Mutant	14 (3.2)	7 (3.2)	7 (3.2)	1.0
Unknown	59 (13.3)	30 (13.6)	29 (13.1)	
Wild-type	369 (83.5)	184 (83.3)	185 (83.7)	
Bevacizumab prescription				
No	229 (51.8)	113 (51.1)	116 (52.5)	0.8
Yes	213 (48.2)	108 (48.9)	105 (47.5)	

Note: Control group, chemotherapy only; experimental group, chemotherapy plus high-dose vitamin C.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.
[a]Weight of patients measured at baseline.

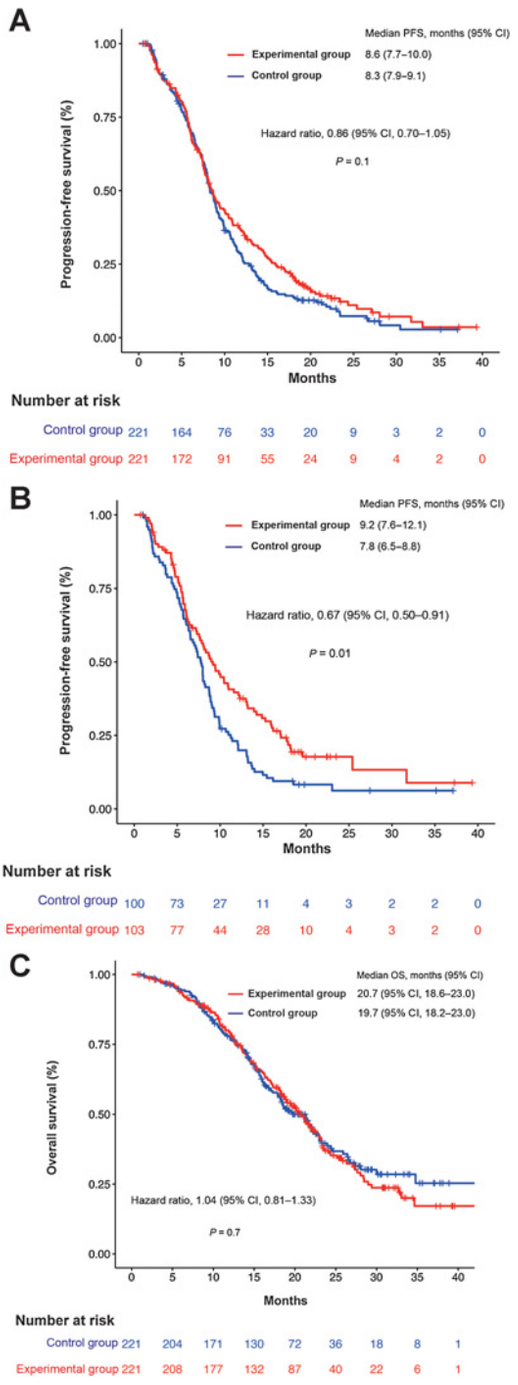

Figure 2.

Progression-free survival (PFS) and overall survival (OS) of patients in the two treatment groups. **A,** PFS of intention-to-treat patients in the two treatment groups. **B,** PFS of intention-to-treat patients with RAS mutation in the two treatment groups. **C,** OS of intention-to-treat patients in the two treatment groups. Control group, chemotherapy only; experimental group, chemotherapy plus high-dose vitamin C.

(HR, 0.64; 95% CI, 0.47–0.87; $P = 0.004$; Supplementary Table S4). Besides, we also observed that in one unplanned subgroup (age ≥55), the PFS of patients with high-dose vitamin C plus chemotherapy was longer than those with chemotherapy only (Supplementary Fig. S1).

PFS rate at 6 months

The 6-month PFS rates were not statistically different between treatment with high-dose vitamin C plus chemotherapy and treatment with chemotherapy only either in the whole cohort (70.0% vs. 70.5%, $P = 0.89$) or in patients with RAS mutation (66.6% vs. 63.6%, $P = 0.55$).

OS

The median OS of the ITT population in the experimental and control group was 20.7 (95% CI, 18.6–23.0) months and 19.7 (95% CI, 18.2–23.0) months (HR, 1.04; 95% CI, 0.81–1.33; $P = 0.7$), respectively (**Fig. 2C**). For patients with RAS mutation, those in the experimental group tended to have longer OS than the control group; however, the difference was not statistically significant (20.2 vs. 16.8 months; HR, 0.79; 95% CI, 0.55–1.13; $P = 0.2$; Supplementary Fig. S3).

Radiographic response

An overall radiographic response, using the RECIST (version 1.1) criteria, was observed in 44.3% (95% CI, 37.7%–51.2%) of patients in the experimental group and 42.1% (95% CI, 35.5%–48.9%) in the control group (**Table 2**). Radiographic assessment was not performed in 6.1% of the patients (27/442). The ORR of patients with RAS mutation undergoing different treatments were not significantly different (Supplementary Table S2).

Safety

TRAEs occurred in 192 of 221 (86.9%) patients in the experimental group and 181 of 221 (81.9%) patients in the control group (**Table 3**; Supplementary Table S5). Grade 3 or higher TRAEs occurred in 74 (33.5%) patients in the experimental group and 67 (30.3%) in the control group. The most common grade 3 or higher TRAEs in the experimental and control groups were neutropenia (14.9% vs. 15.4%), anemia (5.0% vs. 2.3%), leukopenia (3.2% vs. 3.6%), diarrhea (3.2% vs. 2.7%), vomiting (3.2% vs. 1.8%), and intestinal obstruction (2.3% vs. 4.5%), respectively. Eleven patients (5.0%) from the experimental group and 9 (4.1%) from the control group discontinued treatments due to TRAEs.

Discussion

This randomized phase 3 clinical trial showed that high-dose vitamin C plus chemotherapy was not superior to chemotherapy-only as first-line treatment, in terms of PFS, in patients with mCRC and failed to meet its primary endpoint. Any differences in ORR or OS between adding high-dose vitamin C to chemotherapy and chemotherapy alone were insignificant despite observing numerical trends. On the other hand, favorable safety and tolerability profiles were demonstrated by combining high-dose vitamin C with chemotherapy.

Approximately 30% of patients in each group received maintenance therapy after chemotherapy, which was associated with PFS prolongation (Supplementary Fig. S4). Regarding the comparable proportions of maintenance therapy in two treatment arms as well as the consistent findings when stratified upon with or without maintenance therapy (Supplementary Fig. S1), the influence of maintenance therapy over

Table 2. Efficacy and best response of patients in different treatment groups.

	Experimental group ($N = 221$)	Control group ($N = 221$)	*P*
Efficacy			
ORR	98	93	0.9
% (95% CI)	44.3 (37.7–51.2)	42.1 (35.5–48.9)	
DCR	186	180	0.7
% (95% CI)	84.2 (78.5–88.6)	81.4 (75.6–86.2)	
Best response, *n* (%)			0.9
PR	98 (44.3)	93 (42.1)	
SD	88 (39.8)	87 (39.4)	
PD	22 (10.0)	27 (12.2)	
NE	13 (5.9)	14 (6.3)	

Note: Control group, chemotherapy only; experimental group, chemotherapy plus high-dose vitamin C.
Abbreviations: DCR, disease control rate; NE, not evaluated; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

efficacy differences between the two treatment arms may be minimal if any.

Potential beneficial effects of high-dose vitamin C were observed in patients with RAS mutation, supporting the findings from a previous preclinical study that showed selective killing effects of high levels of vitamin C in colorectal cancer cells harboring RAS mutations. It suggested that the oxidized form of vitamin C, dehydroascorbate, was the pharmaceutically active agent resulting in an energy crisis and colorectal cancer cell death, and the selective cytotoxicity of vitamin C stemmed from high expression of GLUT1 glucose transporter combined with RAS oncogene-induced glycolytic addiction (19). Patients' selection by RAS testing is therefore recommended in future clinical trial design.

Patients above 55-years-old had some PFS benefits with the addition of vitamin C to chemotherapy. A previous study showed that patients aged 65 years and older had a high rate (88%) of vitamin C deficiency (23). A long-term high-dose intake of vitamin C suppresses age-related thymic atrophy and maintains immune cells in vitamin C-deficient aged mice model (24). Several studies also found associations between vitamin C levels and cognitive performance in the elderly population (25). It would be interesting to investigate the anticancer role of vitamin C in elderly patients with solid cancer in a prospective study.

The safety profile of high-dose vitamin C in this current trial was consistent with that observed with vitamin C across multiple tumor types (9). Retrospective studies and phase 1/2 trials indicated that the addition of intravenous vitamin C did not further increase toxicities compared with the chemotherapy alone or even improve the quality of life of patients with advanced cancer (17, 18, 26). These studies used relatively lower doses of vitamin C than the present study did. In a phase 3 setting, we observed that patients treated with high-dose vitamin C plus chemotherapy generally had similar TRAEs rates to those with chemotherapy only; moreover, they were mostly grade 1 to 2 AEs and were well tolerated.

There were some limitations of this study. First, the patients received intravenous high-dose vitamin C for 3 days of every treatment cycle, which might not be enough for vitamin C to show its antitumor effect. Considering the synergistic inhibitory effects of vitamin C and oxaliplatin for cancer in patient-derived xenograft models found by our group (20), we conducted a phase I dose-escalation trial of intravenous vitamin C, once daily for 3 days, concurrently with chemotherapy every 14 days. The plasma peak concentration and area under the drug-concentration curve of vitamin C reached maximum values at the current dose (21). Although the current vitamin C dose and dosing schedule indicated good tolerability, there are ongoing phase 2 trials with more infusion days or higher infusion frequency of vitamin C for solid tumors, which could provide more information for this field (27). Second, high-dose vitamin C discontinued at 6 months before the majority of patients progressed, and the true impact of high-dose vitamin C in mCRC may thus be underestimated. Moreover, it would be better to set RAS status as a stratification factor. Although it was hard to anticipate that RAS mutation status would be a good stratification factor, the relatively large sample size and the randomization process should have addressed potential imbalances between the treatment arms in the RAS mutant patients (Supplementary Table S3).

In conclusion, the addition of high-dose vitamin C to chemotherapy as first-line treatment in patients with mCRC did not demonstrate

Table 3. Treatment-related adverse events reported in at least 10% of patients.

Adverse event	All patients ($N = 442$)		Experimental Group ($N = 221$)		Control Group ($N = 221$)	
	Any	≥Grade 3	Any	≥Grade 3	Any	≥Grade 3
Total	373 (84.4)	141 (31.9)	192 (86.9)	74 (33.5)	181 (81.9)	67 (30.3)
Neutropenia	188 (42.5)	67 (15.2)	94 (42.5)	33 (14.9)	94 (42.5)	34 (15.4)
Anemia	173 (39.1)	16 (3.6)	100 (45.2)	11 (5.0)	73 (33.0)	5 (2.3)
Leukopenia	153 (34.6)	15 (3.4)	81 (36.7)	7 (3.2)	72 (32.6)	8 (3.6)
Nausea	87 (19.7)	3 (0.7)	54 (24.4)	2 (0.9)	33 (14.9)	1 (0.5)
Transaminase elevation	86 (19.5)	8 (1.8)	41 (18.6)	6 (2.7)	45 (20.4)	2 (0.9)
Hypoproteinemia	73 (16.5)	0	43 (19.5)	0	30 (13.6)	0
Vomiting	70 (15.8)	11 (2.5)	47 (21.3)	7 (3.2)	23 (10.4)	4 (1.8)
Peripheral neurotoxicity	57 (12.9)	2 (0.5)	23 (10.4)	2 (0.9)	34 (15.4)	0
Thrombocytopenia	52 (11.8)	8 (1.8)	24 (10.9)	4 (1.8)	28 (12.7)	4 (1.8)
Decreased appetite	49 (11.1)	1 (0.2)	30 (13.6)	0	19 (8.6)	1 (0.5)
Diarrhea	47 (10.6)	13 (2.9)	25 (11.3)	7 (3.2)	22 (10.0)	6 (2.7)
Proteinuria	46 (10.4)	0	28 (12.7)	0	18 (8.1)	0
Fatigue	36 (8.1)	0	22 (10.0)	0	14 (6.3)	0

Note: Control group, chemotherapy only; experimental group, chemotherapy plus high-dose vitamin C.

significant improvement in PFS, compared with chemotherapy only, in the overall cohort but may be beneficial for patients with RAS mutation. Taken together, findings from this phase 3 multicenter study provide strong evidence to justify robust and larger clinical trials for combining high-dose vitamin C with chemotherapy for patients with RAS mutant mCRC.

Authors' Disclosures

No disclosures were reported.

Authors' Contributions

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Note

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