Delta Tocotrienol as a Supplement to FOLFOXIRI in First Line Treatment of Metastatic Colorectal Cancer. A Randomized, Double-blind, Placebo-controlled Phase II Study

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Abstract

Purpose Triplet chemotherapy might be more effective than doublet chemotherapy in metastatic colorectal cancer (mCRC), but it may also be marked by increased toxicity. To investigate whether δ-tocotrienol, a vitamin E analogue, with its possible neuroprotective and anti-inflammatory effects reduces the toxicity of triplet chemotherapy, we conducted a randomized, double-blind, placebo controlled trial in mCRC patients receiving first line 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI).

Methods We randomly assigned 70 mCRC patients to FOLFOXIRI plus δ-tocotrienol or FOLFOXIRI plus placebo. FOLFOXIRI was given in eight cycles followed by four cycles of 5-fluorouracil. δ-tocotrienol 300 mg or placebo x 3 daily was added during chemotherapy and for a maximum of two years. The primary endpoint was time to hospitalization or death during treatment with chemotherapy.

Results Median time to first hospitalization or death was 3.7 months in the placebo group (95% CI 1.93-not reached (NR)), and NR in the δ-tocotrienol group (95% CI 1.87-NR) with a hazard ratio (HR) of 0.70 (95% CI 0.36-1.36, p=0.29)). In the placebo group 24 patients (71%) had oxaliplatin dose reductions compared to 17 patients (47%) in the δ-tocotrienol group (p=0.047).

Conclusion The addition of δ-tocotrienol to FOLFOXIRI did not significantly prolong the time to first hospitalization or death compared to FOLFOXIRI plus placebo. Toxicity was manageable and not statistically different between the two groups. There was a statistically significant difference in dose reductions of oxaliplatin pointing to a possible neuroprotective effect of δ-tocotrienol.

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Introduction

Colorectal cancer is still the second leading course of cancer related deaths in developed countries [1]. The overall 5-year survival rate is 55-60% [2]. The combination of two-drug chemotherapy, a fluoropyrimidine and either oxaliplatin or irinotecan, is standard first line treatment of unresectable, metastatic colorectal cancer (mCRC) [3]. Treatment may be further refined using monoclonal antibodies and taking the purpose of treatment into consideration. Treatment goals may be cure after downsizing of metastases, prolonged survival and symptom control [4].

Several studies have suggested exposure of all three types of chemotherapy. In a phase III study conducted by the Gruppo Oncologico Nord Ovest (GONO), 12 cycles of treatment with 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI) showed improved response rate (RR), progression free survival (PFS), and overall survival (OS) as compared to 12 cycles of 5-fluorouracil and irinotecan (FOLFIRI) [5]. Also, the toxicity was manageable. The OLIVIA study comparing bevacizumab in combination with modified FOLFOX-6 (5-fluorouracil and oxaliplatin) or FOLFOXIRI showed improved RR and PFS in the group receiving FOLFOXIRI plus bevacizumab [6]. In the TRIBE study [7], comparing the addition of bevacizumab to FOLFIRI and FOLFOXIRI, respectively, PFS was higher in the group treated with FOLFOXIRI, but there was no significant difference in the resection rate. Compared to trials on FOLFOXIRI without addition of biologically targeted treatment an increased number of grade 3 and 4 adverse events was observed when adding bevacizumab [8].

Triplet compared to doublet chemotherapy may prove more effective in mCRC, but it is marked by increased toxicity leading to hospitalization, dose reduction, postponement, and partly or full discontinuation of treatment [9]. Additional measures to reduce the toxicity of triplet chemotherapy are required.

Tocotrienol is a derivative of vitamin E. The chemical structure of tocotrienol is formed by an aromatic chromanol ring and an isoprenoid chain containing three unsaturated methyl side chains [10]. δ-tocotrienol, a vitamin E analogue, has been shown to affect angiogenesis and stimulate different pathways in in-vitro and in-vivo animal experiments [11]. Other studies have shown that δ-tocotrienol has neuroprotective and anti-inflammatory effects [12, 13], which might reduce the toxic effect of chemotherapy. A reduction in peripheral neuropathy, a well-known potentially chronic side effect of oxaliplatin occurring due to a wide range of molecular and cellular mechanisms [14], could in theory be expected.

The clinical experience of δ-tocotrienol is sparse, but several studies are ongoing [15]. To date, few trials have published data on δ-tocotrienol in humans with cancer, but the toxicity seems minimal or non-existing. In a non-randomized trial in breast cancer, the recurrence rate was reduced when combining tamoxifen and δ-tocotrienol, and there was no toxicity from δ-tocotrienol after five years of treatment [16]. A phase I study used a very high dose of δ-tocotrienol (3.250 mg daily) without signs of toxicity [17]. In a phase II study δ-tocotrienol was given in addition to bevacizumab in chemotherapy refractory recurrent ovarian cancer and suggested an additive effect with no increase in toxicity [18].

To investigate whether δ-tocotrienol with its possible neuroprotective and anti-inflammatory effects reduces the toxicity of FOLFOXIRI, we conducted a phase II trial comparing FOLFOXIRI with and without δ-tocotrienol.

Methods

Trial design and study population

The trial was designed as a single center, randomized, double-blind, placebo-controlled phase II study at the Danish Colorectal Cancer Center South, Vejle Hospital, Denmark. Patients with potentially resectable or non-resectable mCRC eligible for first line treatment were included.

The inclusion criteria were age 18-75 years, ECOG performance status (PS) 0-1 (patients above 70 years were eligible if PS=0), adenocarcinoma in the colon or rectum, evaluable but not necessarily measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [19] and adequate biochemistry. Previous adjuvant chemotherapy for radical treatment of stage II or III colorectal cancer was allowed in patients proven disease-free for more than 6 months. The detailed eligibility criteria are listed in supplementary material (Online Resource 1).

The study was approved by The Regional Committee on Health Research Ethics for Southern Denmark (S-20150185) and the Danish Medicines Agency (2015122439), and was prospectively registered with Clinicaltrials.gov (Identifier NCT02705300). The investigation was conducted in accordance with the Declaration of Helsinki and adhered to the guidelines for good clinical practice (GCP).

All participating patients provided informed consent.

Study data were collected and managed using the Research Electronic Data Capture (REDCap) tool [20, 21] hosted by Open Patient data Explorative Network (OPEN), Odense University Hospital, Region of Southern Denmark. Data were monitored by the regional GCP Unit.

Randomization

A randomization list (1:1) was generated using www.randomization.com and kept at the hospital pharmacy. Via the Clinical Research Unit of Department of Oncology, Vejle Hospital, each patient was assigned a unique code referring to the randomization list. The pharmacy would then allocated the patient to arm A or B. The treating staff and researchers were blinded to the allocation. In case of urgent need for unblinding, the unique codes were kept in sealed envelopes in a locked room in the Department of Oncology.

Treatment and procedures

FOLFOXIRI was given as the standard regimen developed by the GONO group [22] and administered biweekly for eight cycles with irinotecan 165 mg/m^2 i.v for 30 minutes, leucovorin 200 mg/m^2 i.v. for 120 minutes, oxaliplatin 85 mg/m^2 i.v. for 30 minutes followed by a continuous infusion of 5-fluorouracil 3200 mg/m^2 i.v. for 46 hours. After the eight cycles of FOLFOXIRI, treatment was continued with 5-fluoruracil and leucovorin biweekly for four cycles.

Capsules of δ-tocotrienol 300 mg x 3 daily or placebo x 3 daily were administered for a maximum of two years. The tocotrienol capsule consisted of the isomers δ-tocotrienol (90%) and γ-tocotrienol (10%) while the placebo capsule contained olive oil. δ-tocotrienol and placebo were made by the same manufacturer (American River Nutrition, Inc., Hadley, MA, USA) and had the same appearance.

Dose delays and modifications of chemotherapy were permitted based on toxicity and done according to the summaries of product characteristics.

In patients needing an intervention such as surgery or hepatic radiofrequency ablation (RFA) of primary tumor or metastases during study treatment chemotherapy was suspended according to departmental guidelines and δ-tocotrienol/placebo paused 7 days before and after the intervention.

Treatment effect was evaluated by CT scan according to the RECIST 1.1 criteria every eight weeks during chemotherapy, then every three months for a year, every six months the following two years, and yearly the fourth and fifth year after end of chemotherapy. In case of progression, patients were treated according to departmental guidelines.

Blood sampling and biobanking

Before each treatment cycle, blood was sampled for complete blood count, liver function, electrolytes and renal function.

Plasma samples from all patients were collected at baseline, before every treatment cycle and at every follow-up visit for later translational research.

Outcome measures

The primary endpoint was ‘time to first non-planned hospitalization or death’ calculated from start of first cycle of FOLFOXIRI and seven months ahead in order to investigate if δ-tocotrienol reduced toxicity during the planned six months of chemotherapy. Secondary endpoints were number and duration of non-planned hospitalizations during chemotherapy; death during chemotherapy; RR, defined as the proportion of patients achieving partial or complete response according to RECIST 1.1; PFS; OS; radical resection rate; toxicity, and quality of life.

Toxicity assessment

Registration of adverse events was performed before treatment start, before each cycle, after the last cycle of chemotherapy and at every follow-up until progression. Adverse events were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

Quality of life assessment

Quality of life was evaluated by the EORTC QLQ-C30 and EORTC QLQ-CR29 questionnaires before start of treatment, at every response evaluation and follow-up visit.

Statistical analysis

In a previous study with FOLFOXIRI, around half of the patients died or had grade 3-4 toxicities usually requiring hospitalization [5]. Using phase II statistics, we wanted to test if time to first hospitalization or death could be reduced with a hazard ratio of 0.5 by adding δ-tocotrienol to FOLFOXIRI. With a power of 80% and a two-sided significance level of 5%, 70 patients should be included. An enrolment period of 36 months was planned.

Time to first hospitalization or death was calculated and reported according to the Kaplan-Meier method with indication of hazard ratio. PFS and OS were calculated from the day of enrolment as median survival and according to the Kaplan-Meier method. Comparisons were made using hazard ratio and the

treatment arms compared by log rank test. Non-parametric methods were used to calculate and compare number of admissions, response and toxicity. Quality of life was compared using mixed regression models taking into account each patients level and also group difference at baseline.

Statistical calculations were performed using Stata/BE 17.0 (StataCorp LLC, TX, USA).

Results

Between May 6, 2016 and December 19, 2018, 70 patients with metastatic colorectal cancer were randomly assigned to receive FOLFOXIRI plus either δ-tocotrienol (n=36) or placebo (n=34).

Data cutoff was August 1, 2020.

The median age was 64 years (range 40-75 years), 69% had ECOG PS 0, and 39% were female. Age, PS and gender were well balanced between the two arms. Of the total population 67% had primary metastatic disease with 74% and 61% in the placebo and δ-tocotrienol group, respectively. Of note, BRAF mutations known to correlate with a negative prognosis tended to be overrepresented in the δ-tocotrienol group (Table 1).

Patient compliance as to δ-tocotrienol/placebo was monitored by the hospital pharmacy by counting capsules returned. The actual intake of capsules in relation to expected intake was counted by the study nurse at the Department of Oncology. Compliance data were available for 30 and 35 patients in the placebo and δ-tocotrienol group, respectively. An intake of at least 70% of the prescribed capsules was documented for 87% and 80% of the patients in the placebo and δ-tocotrienol group, respectively (p=0.78).

Hospitalization and death

Median time to first hospitalization or death was 3.7 months in the placebo group (95% CI 1.93-not reached (NR)), and in the δ-tocotrienol it was NR (95% CI 1.87-NR) with a hazard ratio (HR) of 0.70 (95% CI 0.36-1.36, p=0.29) (Fig.1). The proportion of patients who were hospitalized or died within seven months from start of treatment was 57% for placebo vs 42% for δ-tocotrienol (p=0.15).

From start of FOLFOXIRI to one month after end of treatment there were 32 hospitalizations in the placebo group and 25 in the δ-tocotrienol group. The mean number of hospitalizations was 0.94 and 0.69, respectively (p=0.35). One patient in the placebo group represented eight of the 32 hospitalizations and in the δ-tocotrienol group one patients had six of the 25 hospitalizations. The median duration of hospitalizations was 5.8 days in the placebo group and 5.9 days in the δ-tocotrienol group (p=0.92).

One of 34 patients (3%) in the placebo group and 2/36 (6%) in the δ-tocotrienol group died during chemotherapy. The patient in the placebo group died from cardiac arrest during 5-FU infusion. The autopsy did not clarify the cause of death further. The patients in the δ-tocotrienol group died from cardiac arrest and cerebral progressive disease, respectively. No autopsy was performed in these patients.

Adverse events

The median number of administered cycles was 12 in both groups. Dose modifications of FOLFOXIRI were done in 24 (71%) and 18 (51%) patients in the placebo δ-tocotrienol group, respectively (p=0.103). Data on postponement of treatment were available for 33 patients in the placebo group and 35 patients in the δ-tocotrienol group. In both groups chemotherapy was postponed in 23 patients (p=0.726). Adverse events data were available for 69 patients. The most common grade 1 and 2 toxicities were nausea, diarrhea, peripheral sensory neuropathy, pain, fatigue, and anemia (Table 2). Grade 3-4 toxicities were uncommon in both groups, except for neutropenia, which occurred in 19 patients (58%) in the placebo group and in 17 patients (50%) in the δ-tocotrienol group. Four patients in each group had febrile neutropenia (11% vs. 12%, p=0.86). There were no grade 3 or 4 peripheral sensory neuropathy in any of the groups. During treatment with FOLFOXIRI the dose of oxaliplatin was reduced in 24 (71%) and 17 (47%) patients in the placebo and δ-tocotrienol group, respectively (p=0.047). The dose was reduced to 75% in 17 and nine patients. Seven patients in both groups had oxaliplatin discontinued. There was no statistically significant difference in the dose reduction of 5-FU or irinotecan between the groups. In general, the adverse events were manageable.

Efficacy

Sixty-five patients (93%) were evaluable for response. One patient died and one had major surgery before the first evaluation. Three patients did not have measurable disease. The response rate was 62% in the placebo group and 52% in the δ-tocotrienol group (p=0.30).

Disease progression occurred in 62 patients (89%) of which 30 (48%) were in the placebo group and 32 (52%) in the δ-tocotrienol group. The median PFS in the placebo group was 9.2 months (95% CI 7.3-10.6) compared to 9.5 months (95% CI 7.4-11.9) in the δ-tocotrienol group (HR 1.08, 95% CI 0.65-1.78, 0=0.77) (Fig.2).

The median duration of follow-up was 33.1 months (95% CI 31.6-35.6). At the time of statistical analysis the median OS was 23.3 months (95% CI 17.1-NR) in the placebo group and 22.3 months (95% CI 17.9-37) in the δ-tocotrienol group, HR=1.1, p=0.76 (Fig.3). The preliminary 3-year survival rate was 41% in the placebo group and 37% in the δ-tocotrienol group.

Radical resection rate

During FOLFOXIRI treatment 16 patients (23%) underwent radical surgery for metastases, i.e. 12 (35%) and four (11%) patients in the placebo and δ-tocotrienol group, respectively (p=0.023). Eight and three patients progressed after surgery.

Quality of life

At baseline 66 of the 70 patients completed quality of life questionnaires. After last cycle of chemotherapy the number was 41. The δ-tocotrienol group scored a little higher at baseline, but overall there was no significant difference between the two groups when comparing changes in General Health Assessment during treatment (p=0.072) (Fig.4).

Discussion

This randomized, double blind, placebo-controlled single center phase II study investigated if the addition of δ-tocotrienol to FOLFOXIRI would improve tolerability defined as the time to hospitalization or death. The combined endpoint of 'hospitalization or death' was chosen due to its robustness, valid registration, manageability, and clinical relevance.

We found a numerically reduced risk over time of hospitalization or death in patients treated with FOLFOXIRI and δ-tocotrienol compared to placebo indicated by an HR of 0.70. This could be of clinical importance, although was not statistically significant (95% CI 0.36-1.36, p=0.29) in this phase II trial powered to detect an HR of 0.50 or less. Interestingly, δ-tocotrienol was associated with fewer dose reductions of oxaliplatin (p=0.047). This supports the potential neuroprotective effect of tocotrienol. A recent study confirms long-term symptoms of polyneuropathy in patients treated with adjuvant oxaliplatin leading to reduced quality of life [23]. Methods to change this are warranted and motivate further studies on δ-tocotrienol for neuroprotection.

The purpose of a phase II trial is to gain insight into a treatment and provide data for dimensioning a possible phase III trial. We suggest a phase III trial with a minimal clinically important difference in hospitalizations and death of HR=0.70 and a secondary endpoint of oxaliplatin induced neurotoxicity.

The dose of δ-tocotrienol in this study was higher than the conventional and recommended use of vitamin E, but we found no toxicity related to δ-tocotrienol and it was well tolerated for up to two years of treatment. This is in agreement with the phase I study using a very high dose of δ-tocotrienol (3.250 mg daily) without signs of toxicity [17].

The observed fewer dose reductions of oxaliplatin in the δ-tocotrienol group did not translate into any difference in efficacy. Of note, the trial was not powered to detect difference in efficacy and all comparisons are prone to type II errors. There was no difference in median PFS; 9.2 months in the placebo group versus 9.5 months in the δ-tocotrienol group. This is in agreement with the phase III trial from the Italian GONO group (9.8 months) [5] and the phase III trial from the Greek HORG group (8.4 months) [8]. There was no difference in median OS between the placebo and the δ-tocotrienol group (23.3 months (95% CI 17.1-NR) and 22.3 months (95% CI 17.9-37), respectively). An antineoplastic or chemosensitizing effect of δ-tocotrienol was not found in this trial as opposed to γ-tocotrienol in in-vitro and in-vivo animal experiments [24]. Median OS was also in agreement with the trials from the GONO and HORG groups.

Since 2010 several trials have been investigating the combination of FOLFOXIRI plus bevacizumab for metastatic, unresectable colorectal cancer [25]. In the TRIBE study [26] comparing FOLFOXIRI and FOLFOXIRI plus bevacizumab, the FOLFOXIRI group had a PFS and OS of 10.0 and 23.6 months, which is comparable to the present study. Adding bevacizumab to FOLFOXIRI improved the survival with a PFS of 12.3 months and an OS 29.8 months. A recent phase II study in chemotherapy refractory ovarian cancer combining δ-tocotrienol and bevacizumab [18] showed higher PFS and OS compared to similar studies suggesting an additive angiogenic effect of δ-tocotrienol to bevacizumab. The angiogenic effect has been seen in in-vitro studies where it suppressed the vascular endothelial growth factor (VEGF) and inhibited proliferation of endothelial cells resulting in reduced tube formation[27, 28]. Our group is exploring the potential synergism between δ-tocotrienol and bevacizumab in colorectal cancer (https://clinicaltrials.gov/ct2/show/NCT04245865)

Curatively intended resection of metastases and/or primary tumor was performed in 23% of patients, which is in agreement with phase II and III trials conducted by the GONO group [29]. Remarkably, there was a statistically significant difference between the groups; 12 patients (35%) in the placebo group had potentially curative surgery compared to 4 patients (11%) in the δ-tocotrienol group (p=0.023). However, the number of patients who underwent surgery is small and did not have an impact on the prognosis. The overrepresentation of BRAF mutations with negative prognostic effect in the intervention group may be of importance in interpreting these results.

The strengths of this study include the fact that it is the first randomized, double-blind, placebo-controlled design to evaluate the potential effect of δ-tocotrienol as to increased tolerability of FOLFOXIRI. Also, the study explored effects of δ-tocotrienol on treatment outcomes in colorectal cancer.

The small study population based on phase II statistics rendering findings preliminary is a limitation of the study, and the results are primarily hypothesis-generating. Another limitation is the single-center setup reducing external validity. Adherence reporting regarding δ-tocotrienol/placebo intake was limited by patients failing to return unused capsules.

Conclusion

In this randomized, double-blind, placebo-controlled trial, we found no significant difference between placebo and δ-tocotrienol in terms of time to first hospitalization or death when given as a supplement to FOLFOXIRI in patients with potentially resectable or non-resectable metastatic colorectal cancer in good performance. δ-tocotrienol 300 mg three times daily was well tolerated. There was a statistically significant difference in dose reductions of oxaliplatin pointing to a possible neuroprotective effect of δ-tocotrienol.

Declarations

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Conflicts of interest: The authors declare no competing interests that could have appeared to influence the work reported in this paper. All authors have completed the ICMJE Disclosure Form.

Availability of data and material (data transparency): Data can be shared for transparency purposes if requested.

Code availability: Statistical calculations were performed using Stata/BE 17.0 (StataCorp LLC, TX, USA).

Authors' contribution statement: Louise Raunkilde, Lars Henrik Jensen and Torben Frøstrup Hansen contributed with conception and design. Lars Henrik Jensen, Torben Frøstrup Hansen, Birgitte Havelund and Caroline Brenner Thomsen collected patient data and reported toxicity. Søren Rafael Rafaelsen and Jan Lindebjerg contributed with acquisition of data. Data analysis and first draft of the manuscript was done by Louise Raunkilde. Lars Henrik Jensen participated in the results analysis and manuscript preparation and supervised the study. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the 1964 Helsinki Declaration. Approval was granted by The Regional Committee of Health Research Ethics for Southern Denmark (S-20150185) and the Danish Medicines Agency (2015122439).

Consent to participate: Informed consent was obtained from all participants included in the study.

Consent for publication: Not applicable

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Tables

Table 1 Baseline patient characteristics

	Total (N=70)	Placebo (N=34)	δ-tocotrienol (N=36)	p-value
Gender - no. (%)				0.66
Female	27 (39%)	14 (41%)	13 (36%)	
Male	43 (61%)	20 (59%)	23 (64%)	
Age, median (range)	64 (40-75)	63.5 (40-74)	64 (41-75)	0.60
ECOG Performancestatus - no. (%)				0.50
0	48 (69%)	22 (65%)	26 (72%)	
1	22 (31%)	12 (35%)	10 (28%)	
Tumorlocation - no. (%)				0.25
Right colon	21 (30%)	7 (21%)	14 (39%)	
Left colon	29 (41%)	16 (47%)	13 (36%)	
Rectum	20 (29%)	11 (32%)	9 (25%)	
Unresected tumor - no. (%)	47 (67%)	25 (74%)	22 (61%)	0.27
Previous adjuvant chemotherapy - no. (%)	6 (9%)	4 (12%)	2 (6%)	0.35
RAS - no. (%)				0.06
Non-mutated	32 (46%)	12 (35%)	20 (56%)	
Mutated	36 (51%)	22 (65%)	14 (39%)	
Not definable	2 (3%)	0 (0%)	2 (6%)	
BRAF - no. (%)				0.14
Non-mutated	54 (77%)	30 (88%)	24 (67%)	
Mutated	13 (19%)	4 (12%)	9 (25%)	
Not definable	2 (3%)	0 (0%)	2 (6%)	
Missing data	1 (1%)	0 (0%)	1 (3%)	
MMR status - no. (%)				0.08
Normal	66 (94%)	34 (100%)	32 (89%)	
Deficient	3 (4%)	0 (0%)	3 (8%)	
Missing data	1 (1%)	0 (0%)	1 (3%)	
Liver-only disease - no. (%)	16 (23%)	6 (18%)	10 (28%)	0.31

Abbrevations: N, number; RAS, KRAS + NRAS; BRAF, BRAF V600E; MMR, mismatch repair

Table 2 Adverse events of special interest, according to treatment groups. Data are n (%).

	CTCAE Grade 0		CTCAE Grade 1		CTCAE Grade 2		CTCAE Grade 3		CTCAE Grade 4		p-value
	Placebo	δ-tocotrienol	Placebo	δ-tocotrienol	Placebo	δ-tocotrienol	Placebo	δ-tocotrienol	Placebo	δ-tocotrienol	
Nausea	6 (18%)	9 (25%)	16 (48%)	21 (58%)	10 (30%)	5 (14%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0.20
Vomiting	16 (48%)	17 (47%)	14 (42%)	17 (47%)	3 (9%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0.99
Stomatitis	16 (48%)	16 (44%)	17 (52%)	16 (44%)	0 (0%)	4 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.43
Diarrhea	8 (24%)	7 (18%)	24 (73%)	21 (58%)	1 (3%)	4 (12%)	0 (0%)	4 (12%)	0 (0%)	0 (0%)	0.12
Constipation	15 (45%)	20 (56%)	17 (52%)	16 (44%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.42
Sensory neuropathy	1 (3%)	3 (8%)	25 (76%)	30 (84%)	7 (21%)	3 (8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.12
Motor neuropathy	23 (70%)	27 (75%)	8 (24%)	9 (25%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.56
Palmarplantar erythrodysaesthesia	27 (82%)	29 (81%)	5 (15%)	7 (19%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.00
Pain	8 (25%)	14 (40%)	19 (60%)	18 (51%)	4 (12%)	2 (6%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	0.18
Anemia	2 (6%)	4 (12%)	17 (52%)	19 (53%)	10 (30%)	11 (30%)	4 (12%)	2 (6%)	0 (0%)	0 (0%)	0.42
Neutropenia	7 (21%)	13 (36%)	1 (3%)	1 (3%)	6 (17%)	5 (14%)	7 (21%)	13 (36%)	12 (37%)	4 (12%)	0.06
Febrile neutropenia	29 (88%)	32 (89%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	3 (8%)	2 (6%)	1 (3%)	0.90
Thrombocytopenia	15 (45%)	18 (50%)	16 (49%)	16 (44%)	1 (3%)	1 (3%)	0 (0%)	0 (0%)	1 (3%)	1 (3%)	0.77
Fatigue	3 (9%)	3 (8%)	26 (79%)	27 (75%)	2 (6%)	5 (14%)	2 (6%)	1 (3%)	0 (0%)	0 (0%)	0.76

Abbrevations: CTCAE, Common Terminology Criteria for Adverse Events

Figures

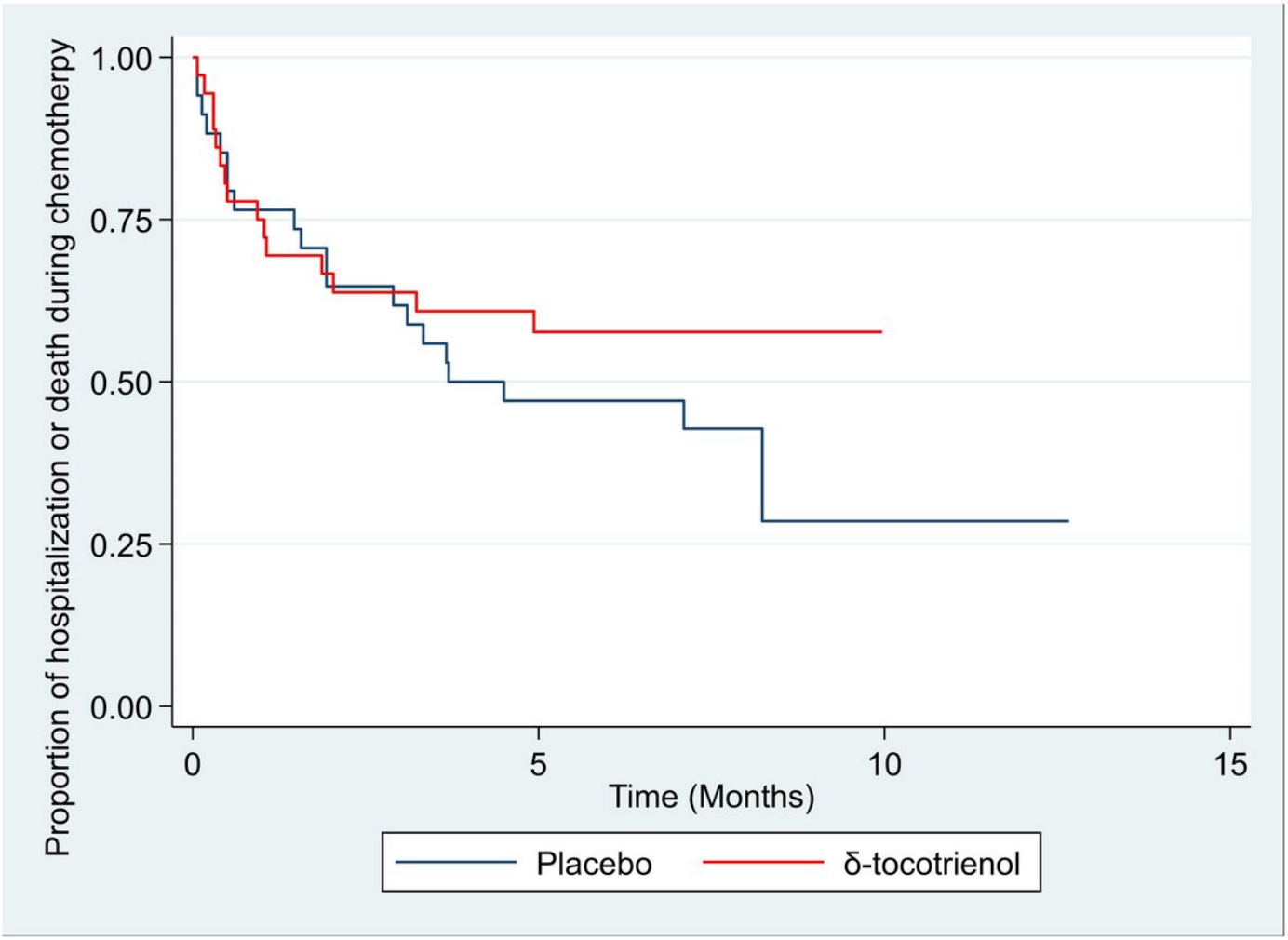

Figure 1

Kaplan-Meier estimate of time to first hospitalization or death according to treatment group. HR=0.70, 95% CI 0.36-1.36, p=0.29

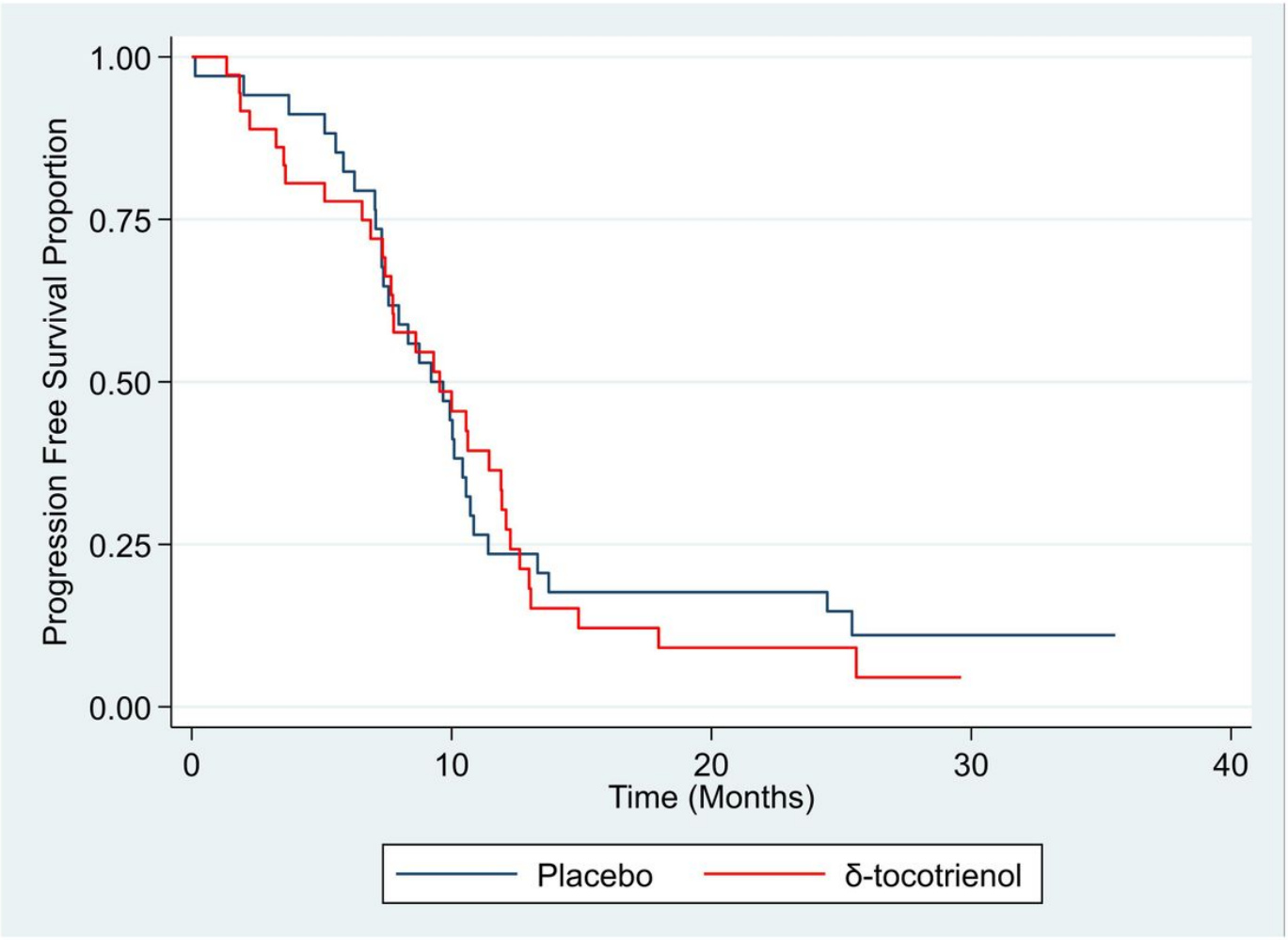

Figure 2

Kaplan-Meier estimate of progression free survival according to treatment group

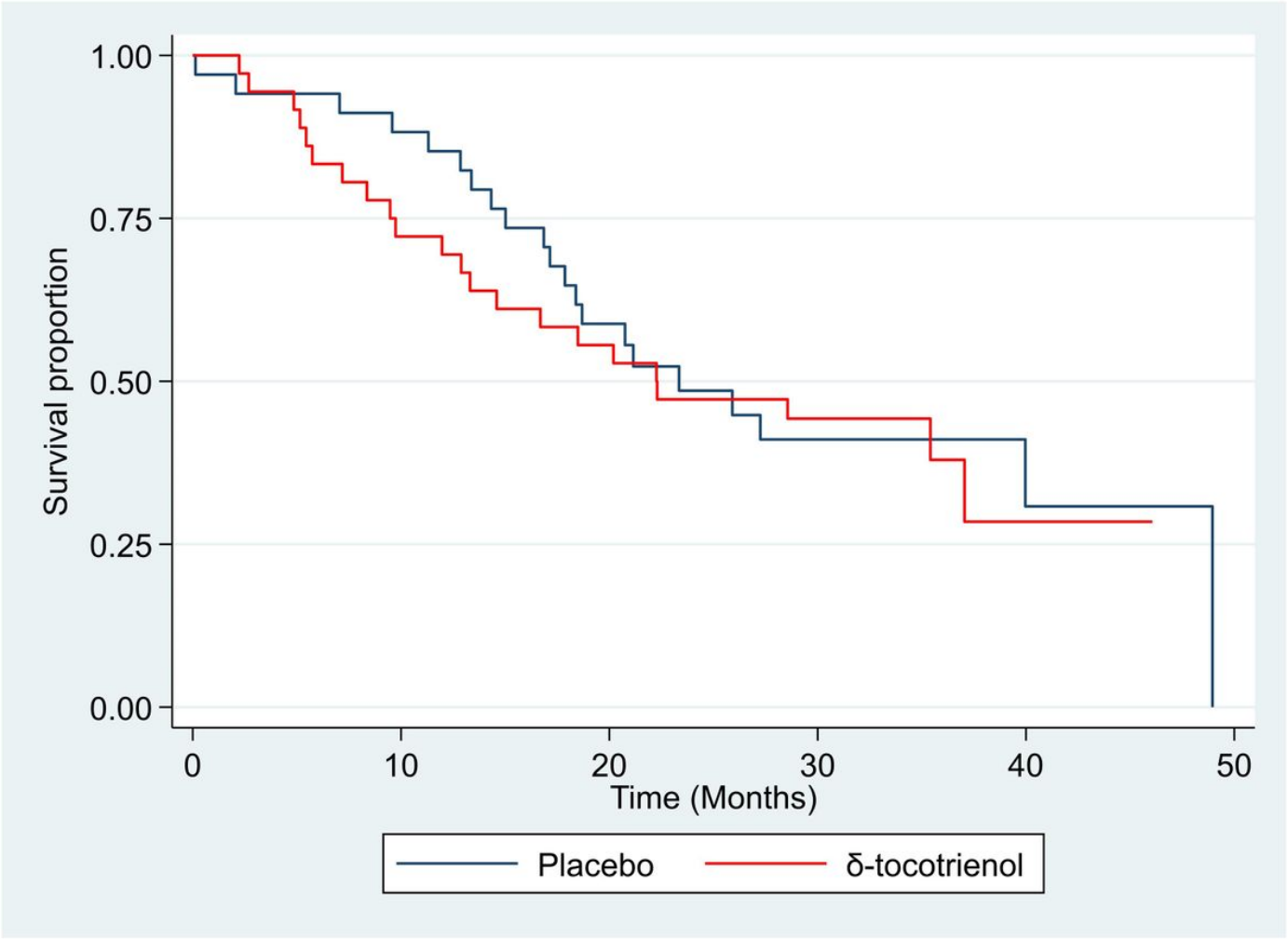

Figure 3

Kaplan-Meier estimate of overall survival according to treatment group

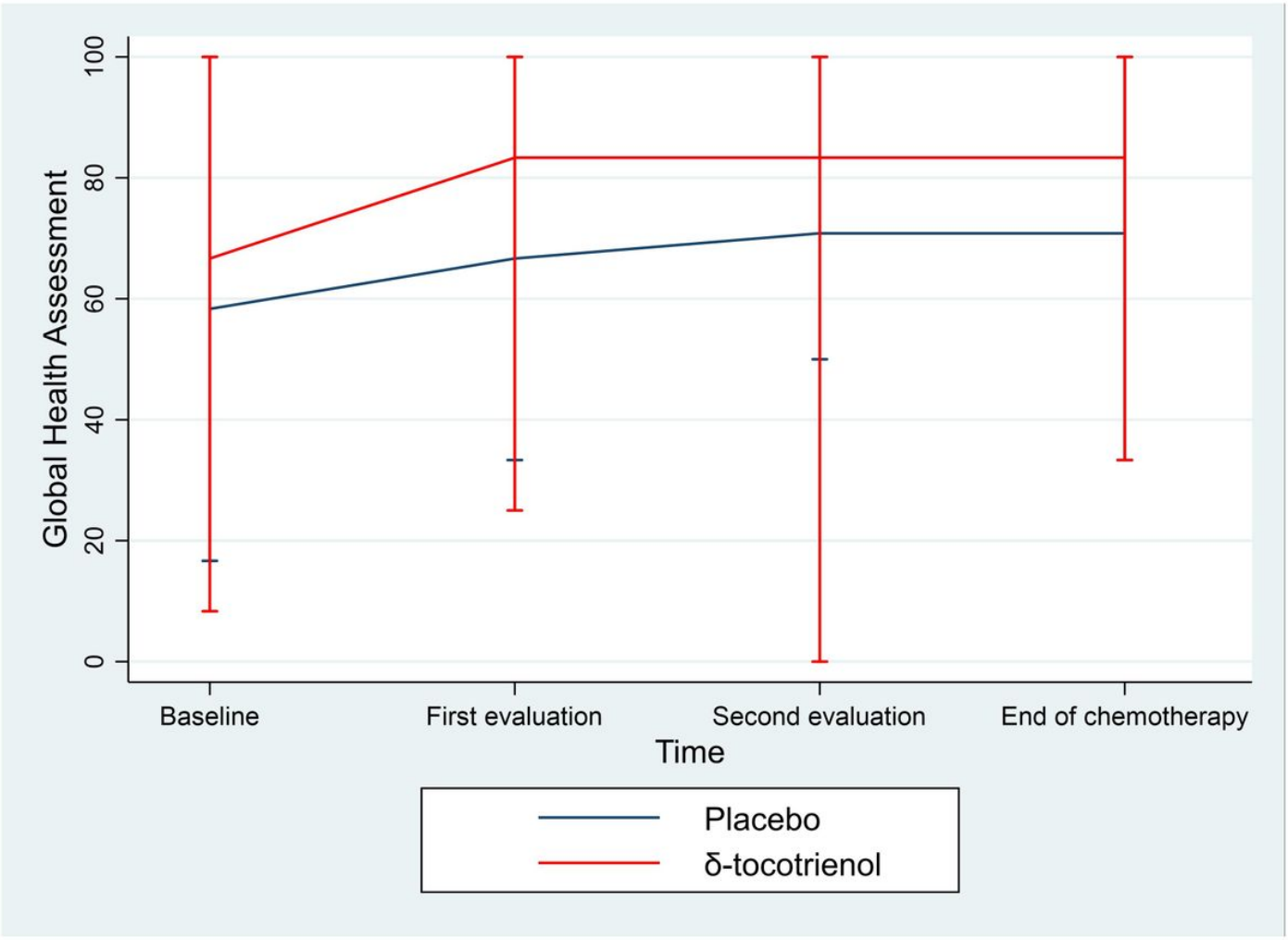

Figure 4

Quality of life during treatment with FOLFOXIRI according to treatment group

Supplementary Files

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- Supplementarymaterial.docx