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Randomized trial of oral cyclophosphamide versus oral cyclophosphamide with celecoxib for recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancer

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ABSTRACT

Background: Oral metronomic chemotherapy, which has low toxicity, has demonstrated promising anti-tumor and anti-angiogenic properties that may lead to prolonged progression-free survival and improved response rates in patients with recurrent epithelial ovarian cancer (EOC). These effects may be enhanced by the co-administration of anti-angiogenic agents.

Methods: We conducted a randomized phase II clinical trial to evaluate the therapeutic benefit of oral metronomic cyclophosphamide (CTX) alone and with the anti-angiogenic drug celecoxib in patients with gynecological malignancies. 52 patients were randomly assigned to two treatments arms: 50 mg oral CTX daily alone (Arm A) or with 400 mg celecoxib twice daily (Arm B). The primary endpoint was response rate. Secondary endpoints included toxicity, time to treatment failure, and overall survival.

Results: In Arm A ($n = 26$), 3 patients (12%) had stable disease >6 months and 1 (4%) had a partial response. In Arm B, 5 (19%) had stable disease >6 months and 1 patient (4%) had a partial response. There were no significant between-group differences in overall survival (9.69 months [95% CI 3.84–13.18] vs. 12.55 months [6.67–17.61]) or in median time to treatment failure (1.84 months [1.68–2.76] vs. 1.92 months [1.64–5.22]). The most common adverse events were nausea, vomiting, and abdominal pain.

Conclusions: Oral metronomic CTX has activity with no major toxicities in heavily pretreated recurrent gynecological cancers and may be considered in patients with indolent disease. We did not observe any additional benefit of celecoxib treatment, though this may be due to small sample sizes.

Introduction

In the United States, epithelial ovarian cancer (EOC) is the fifth most common cancer in women and the leading cause of death amongst gynecological malignancies. It is estimated that 22,530 women will be diagnosed in 2019 and 13,980 women will die from the disease [1]. The primary treatment for EOC consists of aggressive surgical staging and cytoreduction, followed by systemic chemotherapy in virtually all patients. Despite aggressive and often highly toxic [2] therapy, over 75% of patients develop and often eventually succumb to recurrent disease [3].

Cyclophosphamide (CTX) is a cell-cycle non-specific alkylating agent with activity against many solid tumors [4]. CTX plus cisplatin was a standard chemotherapy regimen in ovarian cancer [5] in the early 1990s, before being replaced by cisplatin plus paclitaxel in the mid-1990s and carboplatin plus paclitaxel around 2000.

To minimize side effects while maintaining potency, alternative treatment schedules have been explored. Metronomic dosing of

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standard chemotherapeutic agents, which generally consists of chronic, equally spaced, low doses, has been shown to target the microvasculature in animal models, resulting in significant antitumor activity with tolerable side effects. Tumor growth and metastasis are dependent upon vascularization [6–8], which results from a cascade of molecular and cellular events initiated by the release of angiogenic growth factors [7,9,10]. Pharmacological targeting of the microvasculature has demonstrated anti-tumor activity in several solid tumors [11–13]. Metronomic dosing of CTX has demonstrated clinical benefits in ovarian cancer, with stabilization of disease reported in several case reports and retrospective studies [14–16]. A retrospective Italian study of 54 patients showed an objective response rate of 20.4% with 50 mg oral CTX daily [16], with a majority of responses (72%) observed in platinum-sensitive patients ($n = 34$). Watanabe et al. planned a prospective feasibility study of 50 mg oral CTX twice a day in patients with recurrent EOC. In the heavily pretreated population, 9/14 patients had either a partial response (PR) or stable disease (SD) [17]. However, the study was stopped early due to slow accrual.

Cylcooxygenase-2 (COX-2) is an enzyme involved in the conversion of arachidonic acid to prostaglandins, and its expression is increased in inflammatory states and malignancies [18–23]. Selective inhibitors of COX-2 have been shown to decrease angiogenesis, suggesting the potential utility of these agents in oncology [24,25]. Treatment with selective COX-2 inhibitors induces apoptosis in a variety of cancer cells, including colon, stomach, and prostate tumor cells [26–29]. One mechanism for the pro-apoptotic activity of COX-2 inhibitors is the down regulation of BCL-2, which in turn reduces vascular endothelial cell survival [27]. Celecoxib, a potent and selective COX-2 inhibitor, also induces apoptosis by blocking AKT activation, independent of BCL2 [30], which is a critical signaling pathway for vascular endothelial cell survival [31–34].

Preclinical studies have consistently demonstrated that combinations of anti-angiogenic and chemotherapeutic compounds have synergistic anti-tumor activity [35,36]. A recent meta-analysis [37] showed that in patients newly diagnosed with EOC, the addition of angiogenesis inhibitors to standard chemotherapy can lead to improved PFS; however, improved overall survival (OS) was observed only in patients at high risk for progression (i.e., with FIGO stage IV disease or stage III disease and >1.0 cm of residual disease after debulking surgery). In patients with recurrent EOC, combination treatment with angiogenesis inhibitors and chemotherapy demonstrated improvements in PFS and OS, whereas the administration of angiogenesis inhibitors alone for maintenance therapy showed no significant improvement for either PFS or OS. The combination dose of celecoxib 400 mg oral twice a day and metronomic CTX oral 50 mg daily was chosen because safety and tolerability of this regimen has been demonstrated in prior early phase clinical trials in advanced malignancies [38–40].

Considering the safety, tolerability, and anti-angiogenic properties of both celecoxib and metronomic dosing of CTX, we conducted this phase II clinical trial to test their combined activity and tolerability in patients with recurrent gynecological cancers, including EOC fallopian tube and primary peritoneal cancers.

Materials and methods

Study design and procedures

This was a single center, open-label, randomized phase II study of metronomic oral CTX with or without celecoxib in patients with recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patients were randomly assigned at a ratio of one to one to receive either 50 mg oral CTX daily alone (Arm A) or in combination with 400 mg oral celecoxib twice per day (Arm B). One treatment cycle was defined as 28 days, and treatment continued until disease progression, unacceptable toxicity, or treatment delays for more than 3 weeks. Toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE v2.0). The primary objective of the study was to evaluate the response rate, as assessed by Response Evaluation Criteria in Solid Tumors (RECIST version 1.0). Secondary objectives included evaluation of OS, correlation of PFS with cancer antigen 125 (CA 125) levels in the blood, and the safety profile of CTX in combination with celecoxib.

Table 1
Baseline characteristics of study participants.

Arm descriptions:
Arm A: 50 mg oral cyclophosphamide daily
Arm B: 50 mg oral cyclophosphamide daily + 400 mg oral celecoxib twice daily

	Arm A	Arm B	All patients
Number of eligible patients:	26	26	52
Median age (years):	60 (27–79)	61 (48–80)	61 (27–80)
Median Karnofsky performance status[a]:	90 (70–100)	90 (60–100)	90 (60–100)
Prior treatments:			
Radiation	2 (8%)	3 (12%)	5 (10%)
Chemotherapy	26 (100%)	26 (100%)	52 (100%)
Surgery[b]	21 (81%)	22(85%)	43 (83%)
Histology:			
Adenocarcinoma, not otherwise specified	2 (8%)	2 (8%)	4 (8%)
Clear cell adenocarcinoma	0 (0%)	1 (4%)	1 (2%)
Endometrioid adenocarcinoma	4 (15%)	1 (4%)	5 (10%)
Malignant Mullerian mixed tumor			
Carcinosarcoma	1 (4%)	0 (0%)	1 (2%)
Mixed adenocarcinoma	1 (4%)	0 (0%)	1 (2%)
Serous adenocarcinoma	18 (69%)	22 (85%)	40 (77%)
Site of primary disease:			
Fallopian tube	1 (4%)	0 (0%)	1 (2%)
Female genital tract	1 (4%)	1 (4%)	2 (4%)
Ovary	22 (85%)	25 (96%)	47 (90%)
Peritoneum	2 (8%)	0 (0%)	2 (4%)
Line of therapy prior to enrollment:			
Median (range)	3.5 (1–12)	4 (1–8)	4 (1–12)
1–3	13 (50%)	8 (31%)	21 (40%)
≥4	13 (50%)	18 (69%)	31 (60%)
Platinum resistant?			
Yes	14 (54%)	16 (62%)	30 (58%)
No	4 (15%)	4 (15%)	8 (15%)
Not Applicable	8 (31%)	6 (23%)	14 (27%)
Platinum refractory?			
Yes	1 (4%)	1 (4%)	2 (4%)
No	18 (69%)	18 (69%)	36 (69%)
Not Applicable	7 (27%)	7 (27%)	14 (27%)

[a] Missing performance status data for 6 patients.
[b] Excluding diagnostic procedures.

The study was approved by the Institutional Review board (IRB) of City of Hope and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to inclusion in the study according to institutional guidelines. The protocol was monitored by the City of Hope Data Safety and Monitoring Committee per the institutional guidelines.

Patients

Patients were eligible if they were 18 years or older and had histologically confirmed recurrent or residual epithelial ovarian, fallopian tube, or primary peritoneal cancer. Patient's disease was then sub classified as platinum refractory or resistant cancer. Patients with platinum free interval (PFI) of 6 months or longer were considered to have platinum sensitive disease whereas those with PFI of less than 6 months were considered to have platinum resistant disease. Patients who experience disease progression during first-line platinum therapy were considered to have platinum refractory disease.

There was no limit on prior lines of therapy. Patients with biochemical relapse (defined by Gynecologic Oncology Group criteria as rise in CA 125 with no radiographic evidence of disease) and no

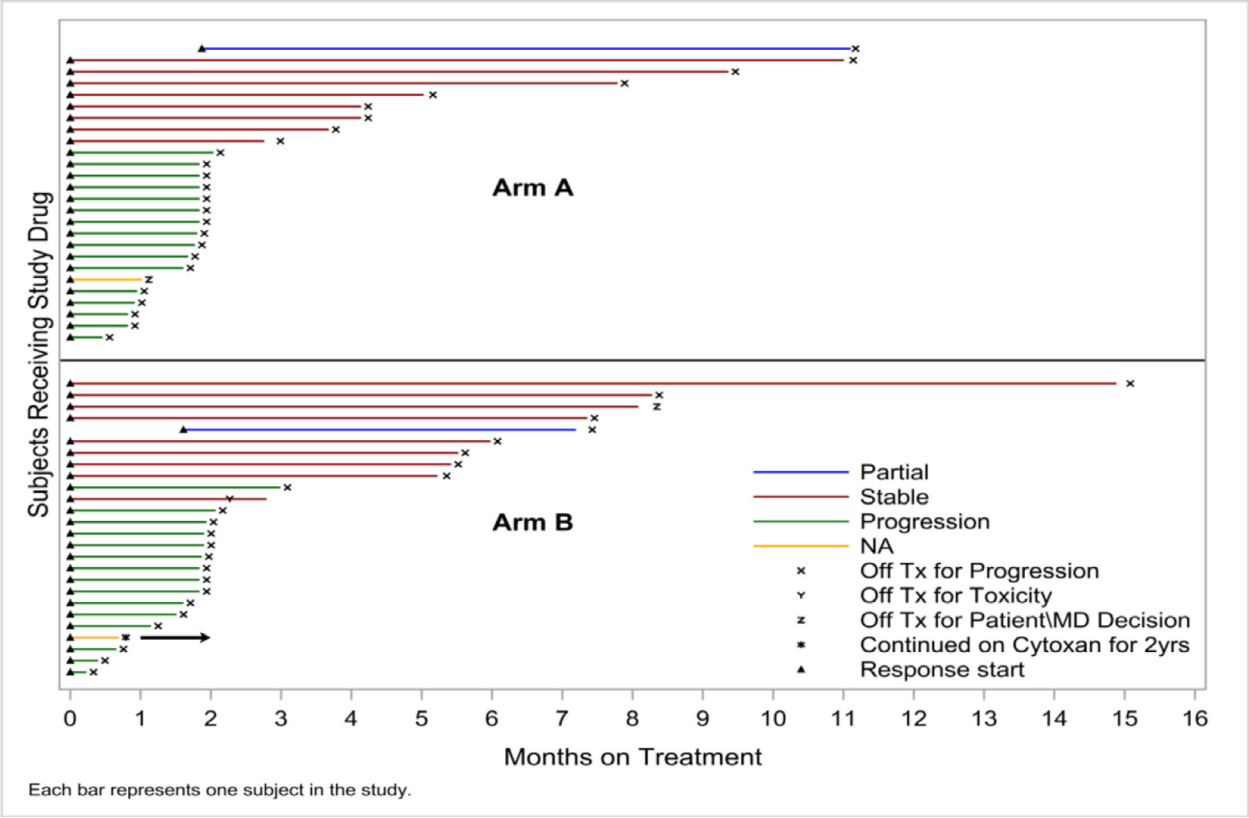

Fig. 1. Summary of patient responses.

Table 2
Best responses of study participants.

	Arm A	Arm B	All patients
Number of patients	26	26	52
Best response			
Partial Remission	1 (4%)	1 (4%)	2 (4%)
Stable Disease	8 (31%)	9 (35%)	17 (32%)
Duration <6 mo.	5 (19%)	4 (15%)	9 (17%)
Duration >6 mo.	3 (12%)	5 (19%)	8 (15%)
Progression	16 (62%)	15 (58%)	31 (60%)
Response not applicable[a]	1 (4%)	1 (4%)	2 (4%)

[a] One patient in Arm A refused treatment after completing course 1. One patient in Arm B went off treatment due to toxicity after completing course 1.

measurable disease and patients with stable brain metastases were eligible. Other key inclusion criteria included: serum creatinine <1.5 mg/dL, adequate bone marrow function as evidenced by an absolute neutrophil count $>1.5 \times 10^9$/L and a platelet count $>100 \times 10^9$/L, Karnofsky performance status of 60–100, and life expectancy of at least 3 months.

Patients were excluded from the study if they had radiotherapy or chemotherapy within 3 weeks prior to the anticipated first day of dosing, unstable or severe medical conditions, active infections, bleeding peptic ulcer within the last 3 months, history of allergic reactions to NSAIDs or sulfa drugs, pregnancy, or significant cardiovascular disease.

Assessment of response and toxicity

Measurable lesions and response assessments were defined according to RECIST (version 1.0). Baseline CA 125 was measured at 3 weeks prior to initiation of study. For response assessment, tumor maker CA 125 was checked each cycle (every 4 weeks) and tumor measurements were done, via imaging, every 2 cycles (every 8 weeks). OS was defined as the time from registration to time of death due to any cause. PFS was defined as the time from registration to the first observation of disease progression or death. Failure free survival was defined as the time from registration to the first observation of discontinuation of treatment. Although the original protocol plan was to report on PFS, we report on failure-free survival due to follow-up limitations on patients who stopped therapy for reasons other than progression such as toxicities and patient choice ($n = 5$). Treatment failure was defined as either discontinuation of therapy, disease progression, or death due to any cause, and failure-free survival was the time to that event.

Statistical analysis

The analysis of each arm of this randomized pilot trial was conducted independently. Responders included patients whose best overall response was a PR, a complete response (CR), or SD. Simon's two-stage minimax design was used for each arm. We assumed that a true response rate >20% would warrant further study for an arm, while a true response rate <5% would not warrant further study. Using this design, the probability of correctly declaring that an arm with a true response rate of 20% warranted further study was 0.80 (power). The probability of falsely declaring that an arm with only a 5% true response rate warrants further study was 0.05 (alpha). For each arm, in the first stage of accrual, 13 patients were enrolled and assessed. If no responses were observed, accrual was to be stopped with the conclusion that the regimen was not promising for further study. Provided that one or more responses were observed in the first 13 evaluable patients, 14 additional evaluable patients were accrued. Responses in 4 or more of the 27 patients would be considered evidence that the regimen warranted further study. Exact 95% confidence intervals calculated for response rates, time to treatment failure, duration of response, and survival were

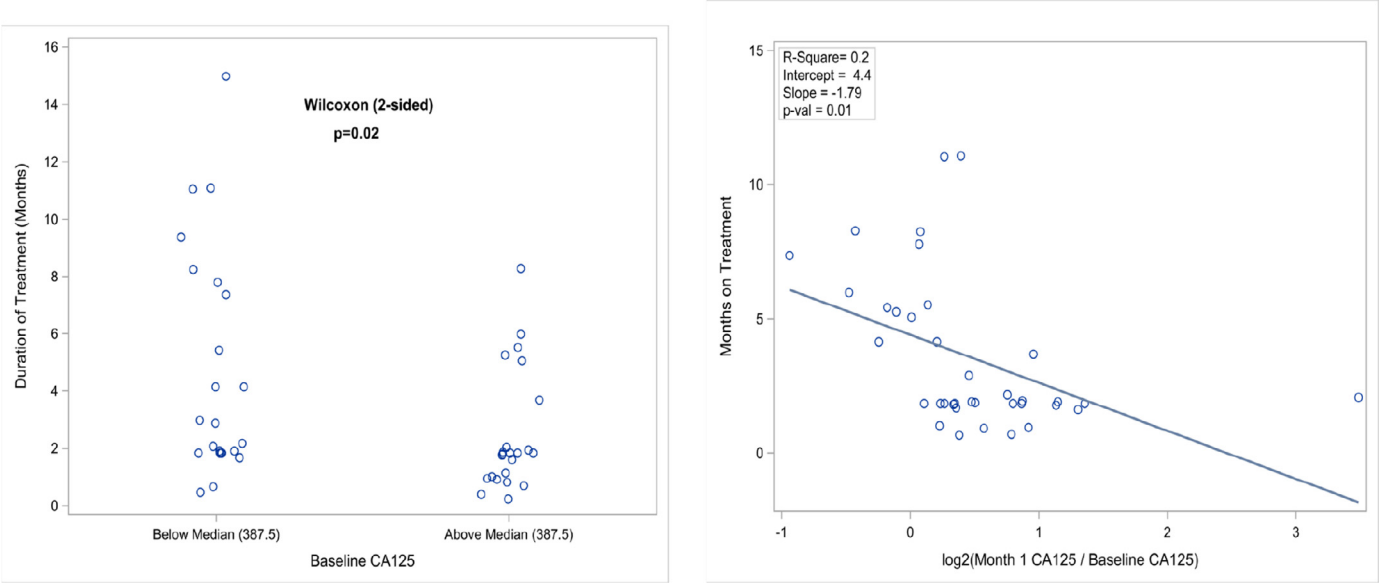

Fig. 2. Correlation of (a) baseline and (b) change in CA 125 with duration of treatment.

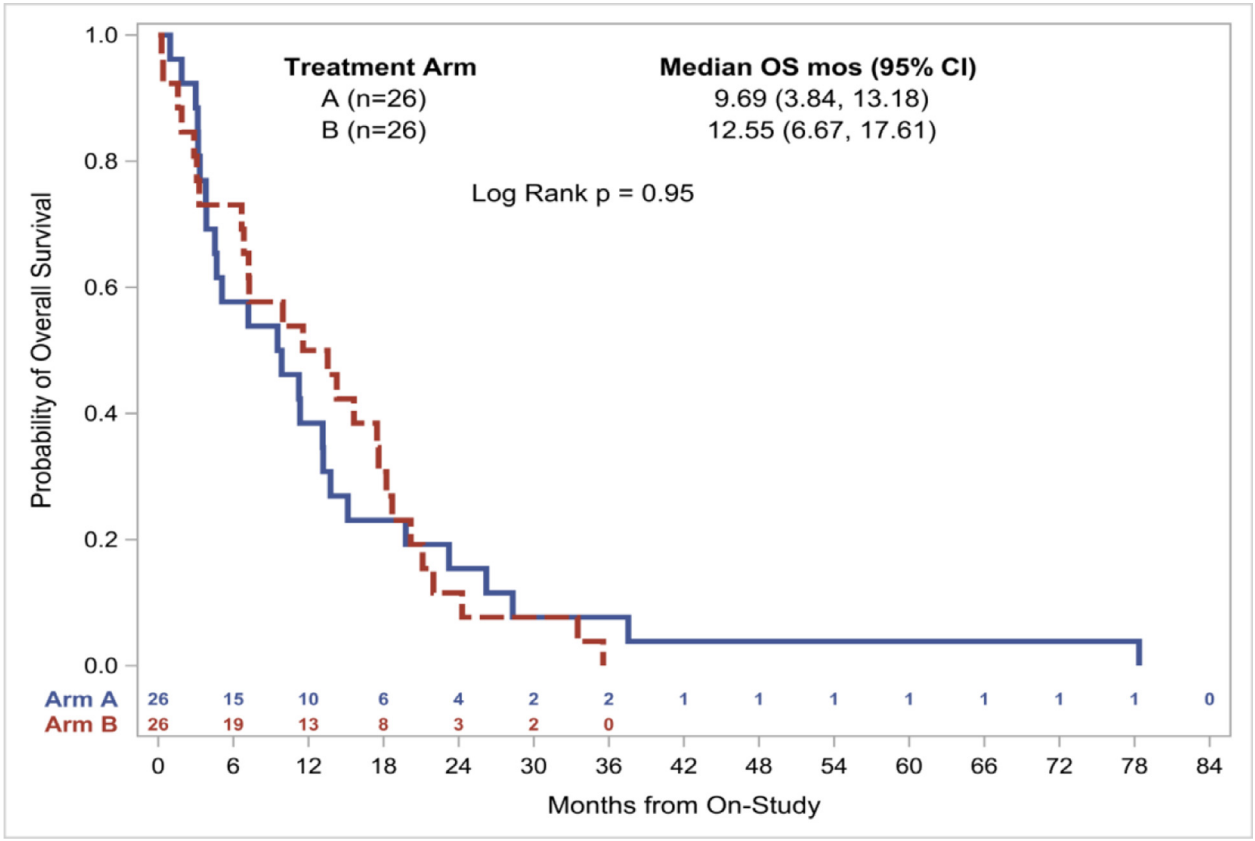

Fig. 3. Overall survival (OS) of patients in treatment arms A and B.

estimated using the product limit method of Kaplan-Meier.

Results

Study population

Patient characteristics are shown in Table 1.The median age was 61 years (range 27–80), and the median Karnofsky performance status score was 90 (range 60–100). 83% of the patients had prior surgery, and 10% had prior radiation therapy. The most common histology was papillary serous carcinoma, present in 77% of the patients. 88% of the patients had primary malignancies of the ovaries, whereas others tumor sites were peritoneum (2%), fallopian tube (2%), subcutaneous soft tissues (4%), and female genital tract (4%). 60% of the patients received 4 or more lines of therapy prior to enrollment in the study, and 58% had platinum-resistant disease at the time of enrollment.

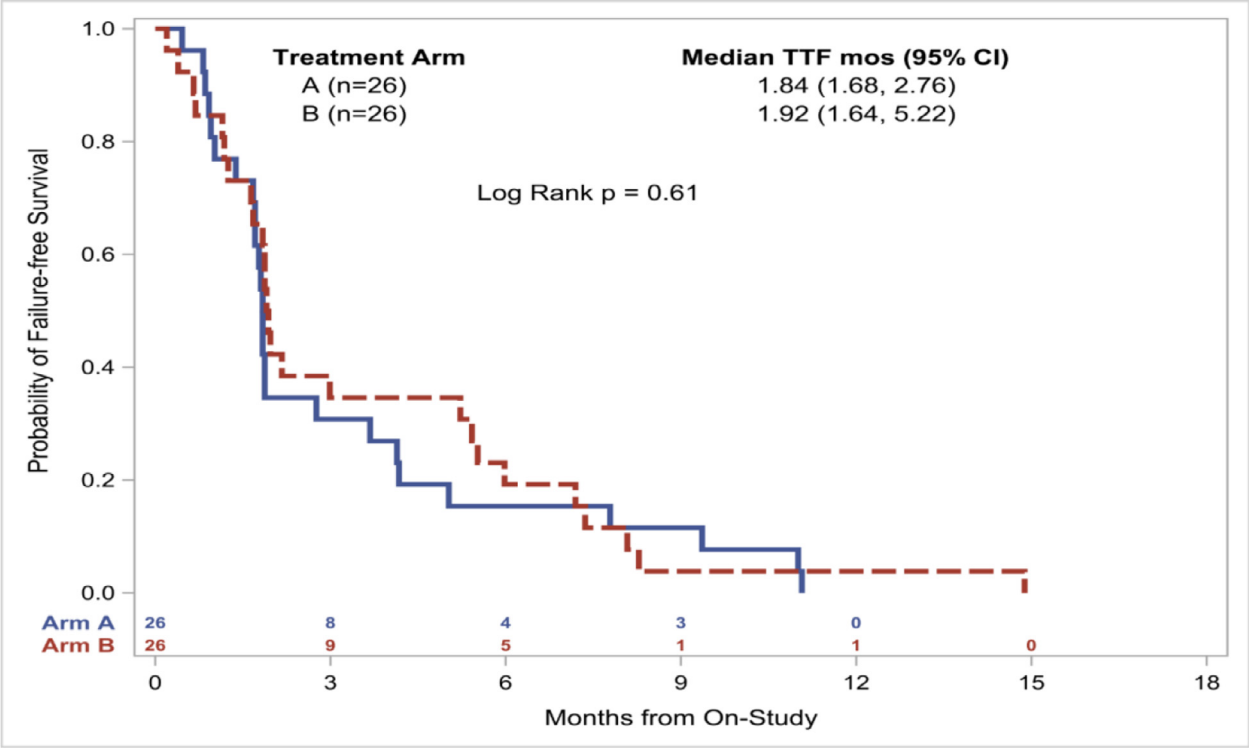

Fig. 4. Time to treatment failure (TTF) of patients in treatment groups A and B.

Table 3
Treatment-related adverse events in study participants.

N^a (%)	Arm A (n = 26)			Arm B (n = 26)		
Adverse event	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Anorexia	5(19%)	–	–	2(8%)	–	1(4%)
Calcium, serum-high	–	–	1(4%)	–	–	–
Fatigue	7(27%)	2(8%)	–	6(23%)	1(4%)	–
Hemoglobin	4(15%)	–	–	4(15%)	2(8%)	–
Lymphopenia	2(8%)	1(4%)	–	5(19%)	–	–
WBC	2(8%)	1(4%)	–	1(4%)	1(4%)	–
Heartburn/ dyspepsia	–	–	–	1(4%)	1(4%)	–
Infection	1(4%)	1(4%)	–	1(4%)	–	–
Muscle weakness, generalized or specific area	1(4%)	1(4%)	–	–	1(4%)	–
Neuropathy: sensory	1(4%)	1(4%)	–	–	–	–
Phosphate, serum-low	1(4%)	1(4%)	–	1(4%)	–	–
Albumin, serum-low	3(12%)	–	–	–	1(4%)	–
Bicarbonate, serum-low	–	1(4%)	–	–	–	–
Dehydration	–	1(4%)	–	1(4%)	–	–
Dyspnea	–	1(4%)	–	1(4%)	–	–
Rash/ desquamation	–	–	–	–	1(4%)	–
Sodium, serum-low	–	–	–	–	1(4%)	–
Pain	6(23%)	–	–	9(35%)	–	–
Nausea & vomiting	7(27%)	–	–	8(31%)	–	–
Diarrhea	5(19%)	–	–	2(8%)	–	–
Hyperglycemia	4(15%)	–	–	1(4%)	–	–
Constipation	1(4%)	–	–	2(8%)	–	–
Edema	1(4%)	–	–	2(8%)	–	–

[a] At least one grade 3 or above or at least two grade 2 in any combination of arms.

Efficacy

The swimmers plot in Fig. 1 depicts when patients responded, as well as when and why patients came off of treatment. Best response data are summarized in Table 2. In Arm A, 3 patients (12%) had SD >6 months, and 1 patient (4%) had a PR. In Arm B, 5 patients (19%) had SD >6 months, and 1 patient (4%) had a PR. We found that 2 of 7 patients with SD in Arm A were progression-free for >6 months, and 3 of 8 patients with SD in Arm B were progression-free for >6 months. One patient in Arm B had prolonged SD and remained on the treatment for 15 months. Across the two arms, patients with higher than median baseline CA 125 levels were on treatment for a shorter duration than patients with lower than median baseline CA 125 levels (1.87 months vs. 2.93 months, $p = 0.02$), as shown in Fig. 2(a). Additionally, reduced CA125 levels after 1 month of treatment correlated with longer treatment durations ($p = 0.01$), as shown in Fig. 2(b).

Median OS was not significantly different between groups: 9.69 months (95% CI 3.84–13.18) in Arm A compared to 12.55 months (95% CI 6.67–17.61) in Arm B (Fig. 3). Additionally, time to treatment failure was not significantly different between groups: 1.84 months (95% CI 1.68–2.76) in Arm A compared to 1.92 months (95% CI 1.64–5.22) in Arm B (Fig. 4). Progression free survival was not significantly different between groups: 1.84 months (95% CI 1.17–3.68) in Arm A compared to 2.02 months (95% CI 1.68–5.42) in Arm B (Supplemental Fig. 1). 48 of 52 patients (92%) discontinued the study due to progressive disease (Fig. 1). One patient was involuntarily withdrawn due to early death, two patients discontinued due to patient/MD decision (one had to undergo surgery), and one patient came off treatment at 21 days due to toxicity but continued on single-agent CTX (off protocol) for 2 years (Fig. 1).

Safety

Treatment-related adverse events are listed in Table 3. The most common grade 2 toxicities in Arm A were fatigue (27%), abdominal pain (23%), nausea/vomiting (27%), diarrhea (19%), hyperglycemia

(15%), hypoalbuminemia (12%), anemia (15%), and sensory neuropathy (4%). The most common grade 2 toxicities in Arm B were abdominal pain (35%), nausea/vomiting (31%), fatigue (23%), and anemia (15%). Treatment was well-tolerated overall with minimal grade 3–4 toxicities. In Arm A, 1 patient had grade 4 hypercalcemia, and in Arm B, 1 patient had grade 4 anorexia. Grade 3 toxicities included fatigue (8% in Arm A and 4% in Arm B), anemia (8% in Arm B), dyspepsia (4% in Arm B), infection (4% in Arm A), muscle weakness (4% in both arms), sensory neuropathy (4% in Arm A), low albumin (4% in Arm B), dyspnea (4% in Arm A), and rash (4% in Arm B).

Discussion

Metronomic dosing has been explored as a potential way to minimize the toxicity of chemotherapies while maintaining efficacy. Our trial aimed to analyze the activity of oral metronomic CTX alone and in combination with celecoxib. We observed a slightly longer OS in the combination arm (12.6 vs. 9.7 months, Fig. 3), however, this was not statistically significant. In this small trial, our data suggests that the combination of metronomic CTX and celecoxib did not perform better than single agent CTX. It is possible that out study was underpowered to detect a small but statistically significant difference between the treatment arms. Also, we enrolled a heterogeneous population of heavily pre-treated ovarian cancer patients with a high frequency of chemo-resistant disease unlikely to respond to another line of chemotherapy. Despite this, we still observed clinical and biochemical responses. Our trial showed that 10 patients (19%) experienced clinical benefit upon treatment with CTX alone or in combination with celecoxib (4% had a PR and 15% had SD >6 months). Best response to treatment was observed in a patient treated in Arm B, who had SD for 15 months.

Several factors may contribute to treatment responses, and we endeavored to identify predictive factors for response common among treatment responders. Subgroup analysis showed that patients with baseline CA 125 levels below the median CA 125 for all patients (387.5 mg/dL) had longer treatment durations than those with CA 125 levels above the median. In addition, there was a statistically significant correlation between decrease in CA 125 levels after 1 month of treatment and the median duration of treatment ($p = 0.01$). These correlations are concordant with previously published data showing improved survival in patients whose CA125 levels were reduced in response to treatment [41] and suggest that patients with low-burden disease may be better suited for this treatment approach than patients with more aggressive disease.

Unresectable ovarian cancer remains incurable and chemotherapy is palliative to help control disease and extend survival. Due to toxicities of chemotherapy, maintenance therapy has become a more common strategy for many cancers to control disease while maintaining quality of life. Our trial demonstrated activity with metronomic dosing of CTX and was well tolerated in patients with indolent disease. Even though we may not see added benefit of celecoxib, anti-angiogenesis has shown promising results in ovarian cancer. Novel clinical trials incorporating metronomic cyclophosphamide and check point inhibitors [42] or other immunotherapy agents are ongoing and may prove useful in ovarian cancer.

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Conflict of interest

No conflict of interest to be disclosed.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2019.100155.

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