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ORIGINAL ARTICLE

Pharmacodynamic stimulation of thrombogenesis by angiotensin (1–7) in recurrent ovarian cancer patients receiving gemcitabine and platinum-based chemotherapy

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Abstract
Purpose This randomized, double-blind, placebo-controlled Phase 2 study evaluated safety and efficacy of A(1–7) for reduction in Grade 3–4 thrombocytopenia in patients receiving myelosuppressive chemotherapy. Pharmacodynamic activity of A(1–7) in platelet production and retention of scheduled dose intensity were also determined.
Methods Thirty-four patients with ovarian, Fallopian tube, or peritoneal carcinoma receiving gemcitabine and carboplatin or cisplatin were evaluated. Patients were randomized to receive study drug subcutaneously at 100 mcg/kg ($n = 11$), 300 mcg/kg ($n = 13$), or placebo ($n = 10$) following chemotherapy for up to six cycles. Hematologic variables were obtained throughout each treatment cycle.
Results There were no drug-related safety issues. There were no instances of Grade 4 thrombocytopenia in patients who received 100 mcg/kg treatment compared to 6 % of chemotherapy cycles for patients receiving placebo ($p = 0.07$). The maximal percentage increase in platelet concentration from baseline was higher for patients who received 100 mcg/kg A(1–7) compared to placebo ($p = 0.02$). This increase was accompanied by a reduction in the nadir absolute neutrophil count ($p = 0.04$). Relative dose intensity for the combination chemotherapy was higher for patients who received 100 mcg/kg A(1–7) compared to placebo ($p = 0.04$). There were no differences in outcomes for patients receiving 300 mcg/kg dose compared to placebo.
Conclusions A 100 mcg/kg dose of A(1–7) was shown to produce pharmacodynamic effects on peripheral blood platelet counts, preserve planned dose intensity, and reduce Grade 3–4 thrombocytopenia following gemcitabine and platinum chemotherapy. These findings are consistent with A(1–7)-induced stimulation of thrombogenesis in the bone marrow following marrow-toxic chemotherapy.

Keywords A(1–7) · Gemcitabine · Carboplatin · Cisplatin · Thrombocytopenia · Thrombocytosis

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Introduction

The renin-angiotensin system (RAS) plays an important role in the regulation of hematopoiesis and the development of hematopoietic progenitors [1]. Every component of the RAS evaluated is contained within bone marrow:

mRNA for angiotensinogen, renin, ACE, AT_{1a}, AT_2, and ACE_2 [2, 3]. Peptides of the RAS are potent stimulators of early progenitor cell proliferation; these cells can then evolve into more specialized cells [4–7]. RAS receptors are increased after injury [7–11]. Recently, it was shown that hematopoietic progenitor cells are most sensitive to A(1–7) and the effect of this peptide in vivo is most robust after injury [2, 4, 5, 8, 10, 11]. The earliest marker for the isolation of hemangioblasts, hematopoietic stem cells, and epidermal stem cells is an angiotensin-converting enzyme 1 (ACE_1; CD143) [10, 12–14]. Most recently, ACE_1 was shown to be expressed in all presumptive and developing blood-forming tissues of the human embryo and fetus: paraaortic splanchnopleura, yolk sac, aorta-gonad-mesonephros, liver, and bone marrow [15]. Preferential induction of the AT_2 receptor directs the hemangioblast toward the hematopoietic lineage [10].

Angiotensin 1–7 [A(1–7)] is a non-hypertensive peptide produced from the cleavage of the C-terminal tripeptide of angiotensin I by neutral endopeptidase or from angiotensin II by ACE_2 [16]. Data from preclinical studies demonstrates the effectiveness of A(1–7) in accelerating multilineage hematopoietic recovery following both whole body radiation and chemotherapy-induced myelosuppression [4, 5, 17, 18]. Administration of A(1–7) in vivo following chemotherapy or irradiation-induced myelosuppression increased numbers of hematopoietic progenitor cells in the bone marrow and formed elements in the peripheral blood, with the most profound effect seen in platelets [4–6, 17, 18]. This increased sensitivity of more immature cells to the proliferative effects of angiotensin peptides offers unique therapeutic opportunities with the possibility of enhanced tissue regeneration, including the repair of injuries associated with radiation exposure.

An open-label, Phase 1/2a clinical study was previously conducted to compare the effects of TXA127 (A(1–7) formulated as a pharmaceutical for subcutaneous administration) versus filgrastim in patients with newly diagnosed breast cancer receiving doxorubicin and cyclophosphamide for at least 3 cycles following surgical reduction in the primary tumor [11]. TXA127 reduced the frequency and severity of thrombocytopenia, anemia, and lymphopenia compared to filgrastim. In the third cycle, absolute platelet nadirs were significantly higher following TXA127 administration. Following the third cycle, recovery of hemoglobin, lymphocytes, leukocytes, and neutrophils was superior in TXA127-treated patients. To further assess the effects of TXA127 on hematopoietic recovery following chemotherapy, a randomized, double-blind, placebo-controlled study was designed to evaluate the clinical and pharmacodynamic effects of TXA127 on platelet and absolute neutrophil counts (ANC) in patients with recurrent ovarian cancer receiving up to 6 cycles of gemcitabine and a platinum-based chemotherapy.

Materials and methods

This was a dose-finding study in patients with recurrent ovarian cancer for whom treatment options are restricted to myelosuppressive chemotherapeutic agents. The myelotoxic chemotherapy regimen of gemcitabine plus a platinum-based therapy (carboplatin or cisplatin) was selected as it is a recognized regimen in this population [19].

Eligibility

Females aged 18 years or over who had histologically confirmed ovarian, Fallopian tube, or peritoneal carcinoma scheduled to undergo combination chemotherapy with gemcitabine and carboplatin or cisplatin were eligible to participate in this study, provided they met the following major criteria at screening: (1) ECOG Performance Status of $\leq$2 and life expectancy of at least 6 months; (2) adequate bone marrow function as measured by: a white blood cell count $\geq$3,000/mm^3, a neutrophil count $\geq$1,500/mm^3, hemoglobin $\geq$9.5 g/dL, and a platelet count $\geq$100,000/mm^3; (3) adequate renal function as measured by: creatinine $\leq$1.5 times the upper limit normal (ULN) and calculated creatinine clearance $\geq$50 mL/min.

Exclusion criteria included: (1) any clinical or laboratory abnormality $\geq$Grade 2 toxicity; (2) unstable cardiovascular disease or serious heart condition within 3 months of screening; (3) metastatic disease of the bone or CNS; (4) concurrent use of hematopoietic or erythropoietic agents; or (5) prior malignancy other than ovarian, fallopian tube or peritoneal carcinoma with <5 years remission.

Study treatment

Following Institutional Review Board protocol approval and patient signature of an informed consent form, eligible patients were randomized in a 1:1:1 ratio to receive 100 mcg/kg/day TXA127, 300 mcg/kg/day TXA127, or placebo with gemcitabine plus carboplatin or cisplatin. The randomization was stratified by the patients' intended chemotherapy regimen (see below). The Investigator, patient, and Sponsor were blinded to the treatment assignment.

Treatment consisted of up to six consecutive 21-day cycles of one of the following chemotherapy regimens:

Regimen A

- Intravenous cisplatin therapy at a dose between 30 and 50 mg/m^2 (inclusive) given on day 1 of the cycle

- Intravenous gemcitabine at a dose of 800 mg/m^2 given on day 1 after cisplatin and on day 8 of the cycle

Regimen B

- Intravenous gemcitabine at a dose of 1,000 mg/m^2 given on days 1 and 8 of the cycle
- Intravenous carboplatin AUC range of 4–6 given on day 1 of the cycle after gemcitabine

Study drug (TXA127 or placebo) was administered subcutaneously during each treatment cycle once daily for 5 consecutive days following the first chemotherapy agent (days 2–6) and for 7 consecutive days following the second chemotherapy agent (days 9–15). At Baseline, End-of-Treatment, and weekly throughout each treatment cycle, blood specimens were collected for the determination of hematologic variables. Hematologic responses were evaluated based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 3.0.

Assessment of response

Clinical outcomes

The primary efficacy endpoint was the percentage of chemotherapy cycles with NCI-CTCAE Grade 3–4 thrombocytopenia, as defined by platelet counts below 50,000/mm^3. Since the total number of cycles varied among patients, the endpoint was calculated for each patient as follows:

$$(\text{Number of cycles with Grade } 3-4 \text{ thrombocytopenia}/\text{Total number of cycles started}) \times 100.$$

For the purposes of this study, any patient receiving a platelet transfusion was considered to have experienced Grade 3 thrombocytopenia.

Pharmacodynamics

The following parameters were evaluated to assess the pharmacodynamic effects of TXA127 on peripheral platelet counts: nadir platelet count, maximal platelet count, and maximum percentage increase and decrease from baseline.

Dose intensity

The dose intensity result of each chemotherapy regimen was calculated based on methods which account for the effect of treatment delays on the calculated dose intensity [20, 21]. For each subject, the relative dose intensity (actual vs. planned) of each chemotherapy agent was calculated. The average relative dose intensity for each treatment group was determined by averaging relative dose intensity (amount of chemotherapy given/amount of chemotherapy scheduled) for individual patients assigned to the specific cohort. These results were used to identify major differences among the treatment groups for the dose intensity of each chemotherapy regimen administered.

Statistical analysis

Thirty-two patients who underwent randomization were included in the efficacy analysis according to their randomly assigned treatment group (intention-to-treat principle). Two additional patients were excluded from this analysis: one patient treated with 100 mcg/kg TXA127 was excluded due to consent withdrawal and one patient treated with 300 mcg/kg TXA127 was excluded due to disease progression. Both patients initiated a single cycle of chemotherapy and had no study drug-related adverse events. All patients were included in the safety analysis.

For purposes of the original sample size calculation, the true mean percentage of chemotherapy cycles with at least one episode of NCI-CTCAE Grade 3 or 4 thrombocytopenia was assumed to be 60 % for placebo, 45 % for 100 mcg/kg TXA127, and 30 % for the 300 mcg/kg TXA127 treatment groups. With 25 patients randomized to each treatment group, a one-way analysis of variance has 80 % power to detect such differences in means with common standard deviation of 33 % and one-sided significance level of 0.05 (note: a sample size calculated from such a one-way analysis of variance model was anticipated to serve as a reasonable approximation for an actual analysis based on the Jonckheere–Terpstra test [22]). The clinical, pharmacodynamic, and dose intensity parameters were summarized descriptively by treatment group, with the treatment groups ordered according to the starting dose of TXA127 (0 [placebo], 100, or 300 mcg/kg). Inferential comparisons between treatment groups were made using the Wilcoxon sum-rank test, a nonparametric statistical method. P-values are one-sided without correction for the multiplicity of tests performed. Analyses were performed using SAS (Version 9.1) and StatXact (Version 8).

Results

Patient characteristics

The results reported here represent the final analysis of this study. A total of 75 patients were planned to be enrolled under the original protocol. Feasibility considerations (e.g., slow patient enrollment and lower incidence of Grade 3–4 thrombocytopenia than planned) necessitated early

termination of the study after 34 patients had been enrolled: 10 patients received placebo, 11 patients received 100 mcg/kg TXA127, and 13 patients received 300 mcg/kg TXA127.

One patient received gemcitabine plus cisplatin throughout study participation. All other patients received gemcitabine plus carboplatin, although three of these patients switched to cisplatin mid-study. The median number of chemotherapy cycles was 5 (range 1–6) for placebo, 6 (range 1–6) for 100 mcg/kg TXA127, and 4 (range 1–6) for 300 mcg/kg TXA127.

The treatment groups were balanced with respect to demographic and baseline disease characteristics (Table 1).

Adverse events

Adverse events are summarized in Table 2. The incidence of adverse events was similar among the three treatment groups. Nausea, constipation, and fatigue were the most frequently reported events. Two patients randomized to each group (placebo, 100 mcg/kg, and 300 mcg/kg) discontinued study drug due to a treatment-emergent adverse event.

Table 1 Baseline characteristics of 34 patients with recurrent ovarian cancer receiving gemcitabine + platinum chemotherapy

Characteristic	Placebo ($n = 10$)	100 mcg ($n = 11$)	300 mcg ($n = 13$)	Total ($n = 34$)
Age (years)				
Median	55	61	60	59
Range	27–77	51–66	39–72	27–77
ECOG				
0	6	9	7	22
1	3	1	3	7
2	0	0	1	1
Not reported	1	1	2	4
Ovarian cancer stage at initial diagnosis				
IA	0	0	1	1
IC	1	1	0	2
IIB	0	1	0	1
IIC	1	1	1	3
IIIB	0	1	1	2
IIIC	7	6	8	21
IV	1	1	2	4
Treatment history				
Chemotherapy naïve	0	1	1	2
Single course of chemotherapy	5	3	5	13
Two of more courses of chemotherapy	4	7	7	18
Not reported	1	0	0	1
Baseline				
Platelet count ($\times 10^9$/L)	343	345	319	332
Baseline ANC ($\times 10^9$/L)	4.5	4.9	4.8	4.8

Table 2 Frequency of adverse events occurring in >20 % of any single treatment group for the 34 patients enrolled

Adverse event	Placebo	100 mcg	300 mcg	Total
Nausea	7	7	9	23
Fatigue	8	6	7	21
Constipation	8	7	5	20
Neutropenia	6	5	8	19
Headache	7	5	5	17
Vomiting	6	4	5	15
Back pain	2	5	5	12
Thrombocytopenia	5	5	2	12
Anemia	2	4	5	11
Abdominal pain	5	4	1	10
Dizziness	3	3	3	9
Dyspepsia	3	4	2	9
Hypersensitivity	5	1	2	8
Leukopenia	3	3	2	8
Dyspnea	2	0	5	7
Pyrexia	2	3	2	7
Rash	1	1	5	7
Dysuria	3	2	1	6
Oropharyngeal pain	4	1	1	6
Abdominal distension	0	1	4	5
Arthralgia	3	1	1	5
Cough	3	0	2	5
Epistaxis	3	0	1	4
Decreased appetite	0	3	0	3

Efficacy

The mean percentage of cycles with NCI-CTCAE Grade 3 or 4 thrombocytopenia (primary endpoint for this study) was 20 % (range 0–67 %) for placebo, 12 % (range 0–50 %) for 100 mcg/kg TXA127, and 22 % (range 0–100 %) for 300 mcg/kg TXA127. For patients receiving placebo, 6 % (range 0–33 %) of cycles were complicated by Grade 4 thrombocytopenia. There were no incidents of Grade 4 thrombocytopenia in any cycles for patients receiving 100 mcg/kg TXA127 ($p = 0.07$ versus placebo). Results similar to placebo were observed for 300 mcg/kg TXA127 (Fig. 1).

Pharmacodynamics

The median maximal platelet count measured post-baseline was 362 $\times$ 10^9/L (range 160–688, mean: 399) for placebo,

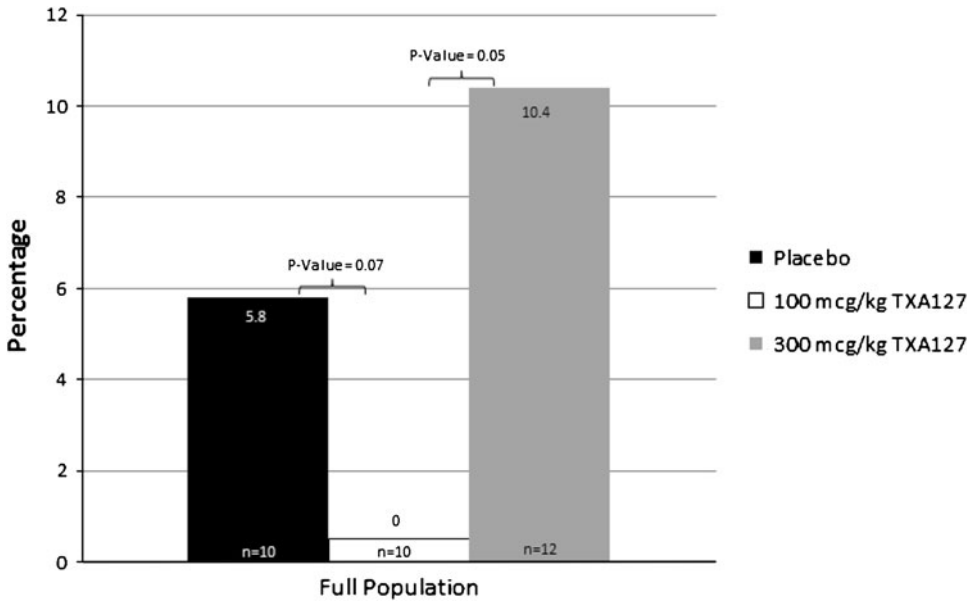

Fig. 1 Percentage of chemotherapy cycles resulting in Grade 4 thrombocytopenia. Patients receiving placebo treatment experienced Grade 4 thrombocytopenia in 5.8 % ($n = 10$) of chemotherapy cycles. In comparison, patients treated with 100 mcg/kg TXA127 [A(1–7)] ($n = 10$) had no Grade 4 thrombocytopenia, while patients receiving 300 mcg/kg TXA127 ($n = 12$) had 10.4 % of chemotherapy cycles affected by Grade 4 thrombocytopenia

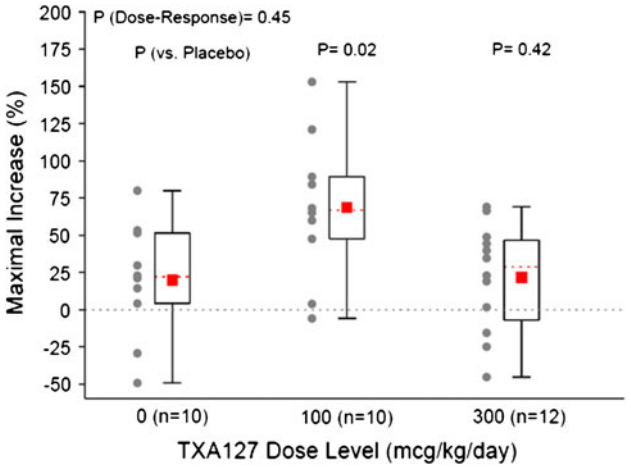

Fig. 2 Maximal percentage platelet count increase from baseline. Median platelet counts in patients treated with 100 mcg/kg TXA127 [A(1–7)] increased by 67 % from baseline levels, while placebo and 300 mcg/kg TXA127-treated patients showed more modest increases of 22 and 29 %, respectively. The difference between 100 mcg/kg-treated and placebo-treated patients was statistically significant ($p < 0.05$)

594×10^9/L (range 372–824 [$p = 0.02$ vs. placebo], mean: 576) for 100 mcg/kg TXA127, and 439×10^9/L (range 223–614, mean 430) for 300 mcg/kg TXA127. The median maximal percentage increase in platelet count post-baseline was 22 % (range: no increase to 80 %, mean: 20 %) for placebo, 67 % (range: no increase to 153 % [$p = 0.02$ vs. placebo], mean: 68 %) for 100 mcg/kg TXA127, and 29 % (range: no increase to 69 %, mean: 22 %) for 300 mcg/kg TXA127 (Fig. 2). The increase in maximal platelet count for 100 mcg/kg TXA127 was accompanied by a decrease in the nadir ANC relative to placebo. The observed maximal percentage decrease in ANC post-baseline was 73 % (range 48–91 %) for placebo, 85 % (range 76–95 % [$p = 0.04$ vs. placebo]) for 100 mcg/kg TXA127, and 78 % (range 48–93 %) for 300 mcg/kg TXA127.

One patient experienced thrombocytosis following administration of 100 mcg/kg TXA127. The principal investigator and medical monitor determined that study drug should be withheld due to the unknown duration of thrombocytosis following study drug discontinuation. As a result, no further study drug was administered and the platelet count returned to normal levels (Fig. 3).

Dose intensity

The median relative dose intensity (actual vs. planned) for the combination chemotherapy administered in this study was 76 % (range 50–100 %) for placebo, 95 % (range 68–99 % [$p = 0.04$ vs. placebo]) for 100 mcg/kg TXA127, and 83 % (range 51–96 %) for 300 mcg/kg TXA127.

Mean maintenance of dose intensity, evaluated as gemcitabine alone and gemcitabine plus platinum-based chemotherapy, was 68 % (without platinum) and 77 % (with platinum) for placebo, 86 % (without platinum [$p = 0.01$ vs. placebo]) and 88 % (with platinum [$p = 0.01$ vs. placebo]) for 100 mcg/kg TXA127, and 77 % (without platinum) and 80 % (with platinum) for 300 mcg/kg TXA127 (Fig. 4).

Discussion

This was a dose-finding study of the safety and pharmacodynamic effects of TXA127 when given concurrently

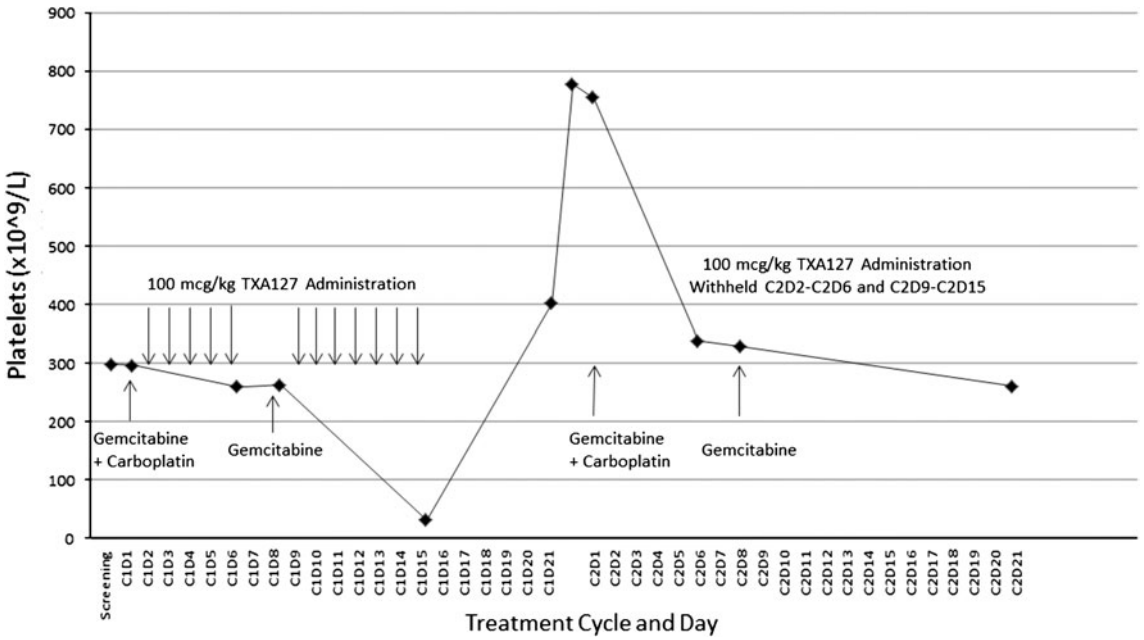

Fig. 3 One patient experienced thrombocytosis following treatment with 100 mcg/kg TXA127. Subject was instructed to discontinue study drug administration for Cycle 2 of chemotherapy. Platelet levels remained within normal limits following chemotherapy without TXA127 administration or blood transfusions

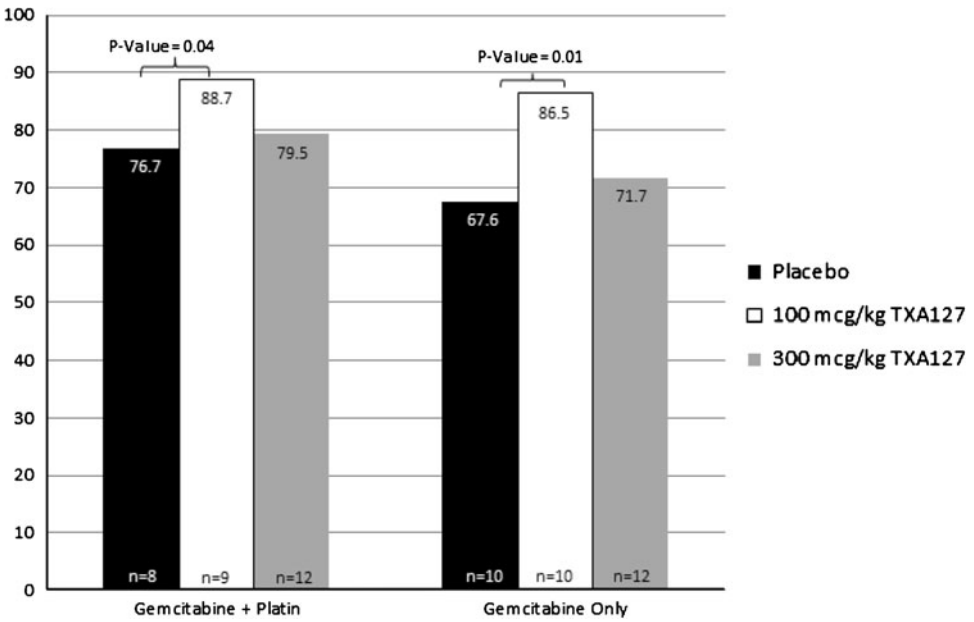

Fig. 4 Maintenance of dose intensity is displayed as the percent of planned chemotherapy delivered to patients. Patients treated with 100 mcg/kg TXA127 [A(1–7)] received, on average, 88.7 % (gemcitabine + platinum, $n = 9$) and 86.5 % (gemcitabine only, $n = 10$) of the intended dose. In comparison, patients treated with placebo received 76.7 % (gemcitabine + platinum, $n = 8$) and 67.6 % (gemcitabine only, $n = 10$). Comparisons between placebo-treated and TXA127-treated patients yielded statistically significant ($p < 0.05$) differences in the 100 mcg/kg group. Number of patients differs due to three patients changing treatment from carboplatin to cisplatin mid-study

with myelosuppressive chemotherapy in up to 6 cycles. The study was stopped due to lower than expected incidence of Grade 3–4 thrombocytopenia in the placebo cohort, as well as changes in clinical treatment practices for recurrent ovarian cancer chemotherapy (increased use of taxane-based regimens) during the course of the study.

Although the overall patient numbers are small, a number of interesting observations were made based on the available data. The safety of TXA127 was demonstrated with these chemotherapy regimens in this patient population. A pharmacodynamic effect of TXA127 at the 100 mcg/kg dose on stimulation of platelet concentrations was shown by (1) absence of Grade 4 thrombocytopenia and (2) a significant increase in platelet concentrations across all chemotherapy cycles. The absence of cumulative myelotoxicity in later cycles of chemotherapy, as evidenced by no increase in graded thrombocytopenia, provides support for future studies evaluating continued marrow responsivity to TXA127 or other marrow stimulants. The significant increase in the maintenance of scheduled dose intensity in the 100 mcg/kg cohort as compared to placebo-treated patients is also consistent with previous preclinical studies which reported enhanced hematopoietic progenitor cell number following A(1–7) therapy [5, 17].

Although the overall number of patients was limited in this study, a modest but significant reduction in ANC was observed in the 100 mcg/kg TXA127 group; this group also had a significant increase in platelet concentrations. These results may have stemmed from a relative increase in chemotherapy exposure due to enhanced maintenance of dose intensity in the 100 mcg/kg TXA127 group, or they may indicate a "lineage steal". Similar observations consistent with "lineage steal" have been reported by Fanucchi et al. [23] and Basser et al. [24] in chemotherapy recipients receiving megakaryocyte growth and development factor (MGDF). The Fanucchi study showed a higher ANC in placebo patients (183 greater per mL; $p = 0.075$) than in MGDF-treated groups. When taken together, these results are consistent with the hypothesis that "lineage steal" may occur when hematopoietic progenitors are pharmacologically stimulated to develop in preferential pathways, as measured by alteration in concentrations of formed elements in the peripheral circulation.

In this study, platelet concentrations were significantly greater in the 100 mcg/kg group compared to the 300 mcg/kg group, consistent with the hypothesis that the stimulation of hematopoietic progenitors can enhance relative sensitivity of the progenitors to chemotherapy. In contrast to a previous clinical study in which there was a 5–7-day period between TXA127 dosing and resumption of chemotherapy, this study only allowed a 48-h hiatus due to the chemotherapy dosing regimen (chemotherapy given on days 1 and 8 of a cycle, with TXA127 given days 2–6 between these treatments). In support of this hypothesis, during the first cycle of chemotherapy, when the sensitization of proliferative progenitors was not a factor, the two doses of TXA127 gave equal platelet responses. The reduction in platelets in 300 mcg/kg TXA127-treated patients was observed in chemotherapy cycles 2–6. Similar results have been reported in preclinical studies following administration of A(1–7) in chemotherapy and radiation models. One study was performed in which A(1–7) was initiated prior to or after chemotherapy [5]. In this study, the white blood cell concentration and bone marrow recovery were reduced if A(1–7) was initiated prior to chemotherapy and continued through chemotherapy. In an unpublished study, initiation of higher doses of A(1–7) during or the day after total body radiation resulted in reduced hematopoietic recovery when compared to lower doses of A(1–7). Others have reported similar observations with radiation (radiation protection vs. radiation sensitization), where hematopoietic response to radiation, including survival, was dependent upon the relative timing of ACE inhibitor administration, a modifier of the RAS, and exposure to radiation [25–27].

Although the small number of patients participating in this trial limits the interpretation of the results, these data taken together with a previous clinical study [11] demonstrate a consistent reduction in thrombocytopenia following TXA127 administration due to direct effects on hematopoietic progenitor cell replication in the bone marrow. The previous clinical trial, conducted in breast cancer patients [11], evaluated lower doses of TXA127 in patients receiving less toxic chemotherapy regimens. Positive thrombopoietic response informed the current study evaluating higher TXA127 doses in more toxic chemotherapy regimens. Results from this study, combined with data from other clinical [11] and preclinical studies [4–6, 17, 18], suggest TXA127 to be a promising candidate for further development as a mitigator of chemotherapy-induced marrow toxicity. Further evaluation of TXA127 in myelotoxic chemotherapy regimens where maintenance of dose intensity has been shown to effect clinical response (e.g. non-small cell lung cancer, uroepithelial cancer, or breast cancer) may prove useful [28].

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Conflict of interest Drs. diZerega and Rodgers are the co-inventors of TXA127.

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