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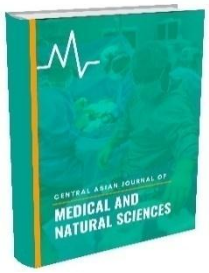

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Separate Results of Metronomic Therapy With Cyclophosphan And Pazopanib in the Palliative Treatment of Recurrent Platinum-Resistant Ovarian Cancer

1. **Shakhanova Shakhnoza Shavkatovna**
2. **Abdurakhmonov Zhurabek Amrilloevich**
3. **Rakhimov Nodir Makhamatkulovich**
4. **Nilufar Aktamovna Talibova**

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[1] Samarkand State Medical University

[2] Samarkand branch of the Republican Scientific and Practical Centre of Oncology and Radiology

[3] Samarkand regional interregional hospice center

[4] Samarkand branch of the Republican Scientific and Practical Centre of Oncology and Radiology

Abstract: Ascites in ovarian cancer is a common complication. Abdominal effusion may occur in the first stage of tumour development, in advanced disease, and may manifest recurrence after radical treatment. If surgery is performed, abdominal flushes and a peritoneal biopsy must be taken to detect malignant cells - it is so common for ovarian tumours to coexist with peritoneal metastases.

Key words: ovarian cancer, metronomic therapy, pazopanib, ascites.

Introduction: Treatment of platinum-resistant recurrent ovarian cancer complicated by ascites is an urgent problem in gynaecological oncology [6, 8]. In platinum-sensitive recurrent ovarian cancer with ascites, the most optimal therapy is the combination of paclitaxel with liposomal doxorubicin and/or gemcitabine+bevizumab [3, 7]. But in platinum-resistant ovarian cancer with recurrence of the disease complicated by ascites the therapeutic options are limited, the results of standard therapies are not comforting. Usually in such cases 2-3 lines of chemotherapy are used, which have many side effects, are moderately and severely toxic, and eventually have a negative effect on the quality of life [2, 5].

Today metronomic chemotherapy (low-dose chemotherapy in continuous mode) gives encouraging results in palliative treatment of many solid tumours [11]

Angiogenesis has been shown to promote tumour growth and metastasis, and RN has been found to be sensitive to anti-angiogenic therapy [4, 9]. Recent studies have shown that oral metronomic therapy (PMT) targets the tumour microenvironment and may also act through an anti-angiogenic mechanism. PMT may act cytotoxically (antiproliferative actions)[1,10]. Angiogenic markers such as VEGF-enothelial growth factor and PDGF-platelet-derived growth factor have been studied in RN tumours and in ascitic fluid by many authors, but with contradictory results.

Objective: to study the separate results of metronomic therapy with cyclophosphan and pazopanib in the palliative treatment of recurrent platinum-resistant ovarian cancer.

Materials and Methods: The study cohort included patients with relapsed ovarian cancer who had previously received up to 6 courses of platinum-containing chemotherapy. Resistance was defined according to the following criteria: disease progression on the background of primary and/or secondary line of platinum-containing chemotherapy. Patients with uncontrolled arterial hypertension, prone to thrombosis, with pathology of coronary arteries, gastrointestinal bleeding in the history were excluded. The study was conducted on the basis of Samarkand regional branch of the Republican Specialised Scientific and Practical Centre of Oncology and Radiology from 2020 to 2023. The total number of patients was 47. The average age was 58±3.7 years. The first group 21(44,7%) received pazopanib 400 mg once daily, with intra-abdominal administration of cyclophosphane. The second group 26(55.3%) received pazopanib 400 mg, cyclophosphane 50 mg once daily from days 1 to 28. In choosing this regimen, we were guided by the following points: cyclophosphamide and anti-VEGF have synergism of action in anti-angiogenic therapy, metranomic therapy with cyclophosphamide reduces the number of CD133+/CD44+/CD24+ cancer stem cells and T-regulatory cells. The vascular normalisation induced by anti-VEGF therapy may also promote the homing of effector T cells, leading to activation of anti-tumour immunity [8]. Antihypertensive therapy, anti-emetics, H2-blockers, and symptomatic therapy were performed as indicated. Toxicity was assessed according to the NCI General Terminology Criteria scale. In case of 3-4 degree toxicity the subsequent dose was interrupted for 2 weeks and resumed, in case of persistent toxicity the therapy was stopped. Pazopanib was reduced to 200 mg. The criterion of efficacy was considered to be lowering of CA-125, reduction of ascites and quality of life.

Results: The frequency of objective responses in both compared groups was similar. In group 1 it was 55%, in group 2 54%. In group 1 complete 29%, partial 26.3%, stabilisation 4.1%, progression 40.1%; in group 2 compared group complete 29.7%, partial 24.3%, stabilisation 5.4%, progression 40.5%, median duration of response was 7.8 months 95% CI 2-22 months**.**

The median progression-free survival was 5.1 months (95% CI 3.1-10.3) in group 2 and 3.4 months (95% CI 3-5m) in group 1. Median overall survival in group 2 was 11.2 months (95%DI 5.6), statistically not reached p=0.03. 21 patients were still on metronomic therapy.

Fourteen (53.8%) patients in group 2 and 10(47.6%) in group 1 experienced adverse events according to NCI criteria. Side effects of 3-4 degree of severity were mainly provoked by pazopanib: mucositis 29,7% p=0.36, fatigue 13,5% s=0.07, arterial hypertension 5,4%, increased activity of liver enzymes 5,4%.

Initial general health status of functional scales was similar in the compared groups. In the first group, the symptom scales at baseline - fatigue, dyspnoea, constipation and diarrhoea were greater. The second group showed significant improvement in the symptoms of nausea, vomiting and besomnia, loss of appetite were observed in the second group

Conclusions: The addition of pazopanib to oral cyclophosphamide to metronomic therapy resulted in improved progression-free survival as well as overall survival with a well-tolerated toxicity profile. There was a moderate improvement in quality of life scores on a symptom scale between the two

groups. Whether checkpoint inhibitors can be combined with metronomic chemotherapy agents is an area of future research.

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