The American Journal of Medical Sciences and Pharmaceutical Research (ISSN – 2689-1026)
VOLUME 05 ISSUE 08 Pages: 77-81
SJIF IMPACT FACTOR (2020: 5. 286) (2021: 5. 64) (2022: 6. 319) (2023: 7. 396)
OCLC – 1121105510
Publisher: The USA Journals

Journal Website: https://theamericanjournals.com/index.php/tajmspr

Research Article

TARGETED THERAPY IN THE PALLIATIVE TREATMENT OF PLATINUM-RESISTANT RECURRENT OVARIAN CANCER COMPLICATED BY ASCITES

Submission Date: August 20, 2023, **Accepted Date:** August 25, 2023,
Published Date: August 30, 2023 |
Crossref doi: https://doi.org/10.37547/TAJMSPR/Volume05Issue08-14

Sh.Sh.Shakhanova
Samarkand State Medical University, Uzbekistan

J.A. Abdurakhmonov
Samarkand State Medical University, Uzbekistan

N.M.Rakhimov
Samarkand Regional Interregional Hospice Centre, Uzbekistan

ABSTRACT

Ascites in ovarian cancer can reach any volume. As a rule, a small effusion without clinical manifestations is not removed, it regresses against the background of systemic chemotherapy. In ovarian cancer ascites is rarely very large, but the abdomen can be huge due to the combination of several litres of fluid with a large mass of tumour. Ascites that interferes with normal life is necessarily evacuated. Due to the accumulation of fluid can cause shortness of breath and swelling of the legs, impaired breathing and nutrition - vomiting just eaten and drunk. In such situations, a laparocentesis must be performed.

KEYWORDS

Platinum resistance, targeted therapy, ovarian cancer, ascites, relapse.

INTRODUCTION

Recent decades have led to revolutionary discoveries in the study of carcinogenesis. One of these discoveries is angionesis in cancer development. The addition of anti-angiogenic therapy (bevacizumab) in platinum drug-resistant ovarian cancer increased response rates by 27-32% and disease progression-free survival (DPS) to 6 months (compared to 4 months with

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
VOLUME 05 ISSUE 08 Pages: 77-81
SJIF IMPACT FACTOR (2020: 5. 286) (2021: 5. 64) (2022: 6. 319) (2023: 7. 396)
OCLC – 1121105510
Publisher: The USA Journals

chemotherapy alone), but overall survival remained unchanged [6].

Bevacizumab is a drug that is frequently studied as an anti-angiogenic agent in ovarian cancer. Current realities dictate that it would be cost-effective and easy to administer with a similar mechanism of action. Pazopanib is an oral angiogenesis inhibitor acting on several protein kinase receptors - VEGFR, PDGFR, FGFR and c-Kit [1, 11,18]. The preclinical and clinical data conducted indicate the promising efficacy of pazopanib in ovarian cancer. A phase II study by Oaknin A. et al. (2012) evaluated pazopanib monotherapy in patients with recurrent RCC. Patients received pazopanib at a dose of 800 mg per os daily until disease progression. Eleven patients out of 36 (31%; 95% CI, 16-48) had a response in the form of CA-125 downregulation. 20 patients (56%) showed stabilisation. 12, 13].

In the AGO-OVAR-16 study, maintenance therapy with pazopanib for 24 months after completion of first-line therapy with platinum drugs improved VBP by 5.6 months compared with placebo. [8,15]. However, as shown in the updated analysis of this study, there was no improvement in OBP.

PURPOSE

To study the long-term results of metronomic chemotherapy and targeted therapy in the palliative treatment of platinum-resistant ovarian cancer

MATERIALS AND METHODS

Platinum resistance was defined as disease progression (metastasis and/or recurrence) within 6 months of completing the last cisplatin or carboplatin-based therapy with or without bevizumab. Malignant ascites was diagnosed by laparocentesis followed by exfoliative cytological examination of the fluid. In case of ineffective treatment with platinum-containing regimen, we orally administered cyclophosphamide (Endoxan) and pazopanib with ECOG performance status of 1-2 points. Patients were administered as follows: pazopanib tablets (600 mg/day orally in 2 doses, 400 and 200 mg) and cyclophosphamide (50 mg/day orally for 21 days every 28 days) until disease progression or unacceptable toxicity. We used cyclophosphamide in a manner that reduces the incidence of myelosuppression and reduces the cumulative dose that patients receive in the long term [14, 15]. Clinical, radiological and serological responses were evaluated every 12 weeks. Dose reduction was performed for grade 3 or 4 toxicity. The first reduction involved reducing the dose of pazopanib to 200 mg twice daily, and the second reduction involved reducing the dose of pazopanib to 200 mg once daily. Side effects that usually required dose reduction were diarrhoea, palpebral plantar syndrome, fatigue, mucositis and transaminitis The choice of this regimen was due to the fact that metronomic cyclophosphamide and anti-VEGF therapy may be the result of synergism of their anti-angiogenic actions; metronomic cyclophosphamide reduces the number of CD133+/CD44+/CD24+ cancer stem cells and T-regulatory cells. Vascular normalisation induced by anti-VEGF therapy may also promote the homing of effector T cells, leading to activation of antitumour immunity [2,5].

We used this treatment regimen when patients showed treatment failure with standard therapy. To the best of our knowledge, this regimen is not approved for the treatment of ovarian cancer, and its use in our patients was off-label.

Detailed baseline patient characteristics are listed in Table 1.

The American Journal of Medical Sciences and Pharmaceutical Research
(ISSN – 2689-1026)
VOLUME 05 ISSUE 08 Pages: 77-81
SJIF IMPACT FACTOR (2020: 5. 286) (2021: 5. 64) (2022: 6. 319) (2023: 7. 396)
OCLC – 1121105510
Publisher: The USA Journals

TABLE 1.

Baseline characteristics

Age	
Average	54
Range	40-60
ECOG Status	
1	7(23,3%)
2	23(76,7%)
Histological appearance	
Serous adenocarcinoma	4 (13,3%)
Light-cell adenocarcinoma	26(86,7%)
Number of chemotherapy treatments	
Up to 4	7(23,3%)
Up to 8	9 (30%)
More than 8	14(46,7%)
Bevizumab	8(26,7%)
Platinum status	
Resistant	21(70%)
Refractory	9(30%)

The mean number of cycles administered was 6 (range 2 to 48 cycles), with 6 patients treated for more than 12 months. One patient with platinum drug-resistant disease continued treatment for 48 months at the time of analysis.

RESULTS

Dose reduction due to toxicity was required in 14 patients (46.6%). The adverse events included fatigue 16(55%), diarrhoea 13 (43.3%), increased liver enzyme activity 15(50%), mucositis 15(50%), myelosuppression 10(33.3%), palmar-podontal syndrome 9 (30%), hair depigmentation 5(16.6%.)) and arterial hypertension 4(13.3%).

At the time of analysis, 5 patients were on therapy, 12 had disease progression, and 3 dropped out of follow-up. Of the treated patients, 9 (45%) had a partial response (including 1 of 3 patients previously receiving bevacizumab), 6 (30%) had disease stabilisation, and the best response was disease progression in 5 (25%).

The American Journal of Medical Sciences and Pharmaceutical Research (ISSN – 2689-1026)
VOLUME 05 ISSUE 08 Pages: 77-81
SJIF IMPACT FACTOR (2020: 5. 286) (2021: 5. 64) (2022: 6. 319) (2023: 7. 396)
OCLC – 1121105510
Publisher: The USA Journals

The median time to VBP was 5.5 months and the median time to OS was 9.5 months

Despite the small sample size, encouraging responses were observed in difficult-to-treat patients (response was observed in 1 patient with clear cell carcinoma, 1 patient with platinum drug-resistant disease receiving therapy for 48 months, and 5 patients treated for at least 12 months).

Patients included in this retrospective analysis were asked to use pazopanib off-label (together with cyclophosphamide) as part of routine clinical practice and their data were later analysed. Off-label use includes the use of a drug in doses, patient populations, indications or routes of administration that are not reflected in the manufacturer's company-approved product labelling [3].

Off-label use of drugs is common in many clinical scenarios such as oncology, paediatrics, psychiatry and intensive care units [9, 16].

In India, it is an acceptable practice, especially for recurrent cancer, to use a drug off-label, provided there is some evidence for its use and the patient is adequately informed that it is not an indication for prescribing along with possible side effects and benefits [16].

In addition, some patients prefer an oral regimen for platinum resistance or refractoriness to platinum. For these reasons, we treated this cohort of patients with pazopanib off-label prior to bevacizumab.

The regimen was reasonably well tolerated. Although dose reduction due to toxicity was required in 70% of patients. Moreover, most patients (55%) required a dose reduction of 33% of the initial dose.

CONCLUSION: The combination of pazopanib and oral cyclophosphamide is a well-tolerated regimen with clinically significant benefit in patients with platinum-resistant or platinum-resistant RL. It can be considered as a treatment option for patients who have undergone intensive treatment.

REFERENCES

1. Рахимов Н. М. и др. МЕХАНИЗМ РАЗВИТИЯ ПЕРИТОНЕАЛЬНОГО ЗЛОКАЧЕСТВЕННОГО АСЦИТА ПРИ РЕЦИДИВЕ РАКА ЯИЧНИКА //Клиническая и экспериментальная онкология. – 2020. – №. 4. – С. 45-49.
2. Anderson R. D. American Society of Hospital Pharmacists. ASHP statement on the use of medications for unlabeled uses //Am J Hosp Pharm. – 1992. – Т. 49. – №. 8. – С. 2-006
3. Bertozzi S. et al. Nanotechnologies in obstetrics and cancer during pregnancy: a narrative review //Journal of Personalized Medicine. – 2022. – Т. 12. – №. 8. – С. 1324
4. Cazzaniga M. E. et al. Metronomic chemotherapy //Cancers. – 2021. – Т. 13. – №. 9. – С. 2236.
5. Colombo N. et al. ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease //Annals of Oncology. – 2019. – Т. 30. – №. 5. – С. 672-705.
6. Dzhurayev M. D. et al. Key Priorities For Immunohistochemical Testing In Predicting Cervical Cancer Recurrence //The American Journal of Medical Sciences and Pharmaceutical Research. – 2021. – Т. 3. – №. 06. – С. 87-93.
7. duBois A. et al. A Phase III //Randomized, Double-Blind Trial of Pazopanib Versus Placebo

The American Journal of Medical Sciences and Pharmaceutical Research (ISSN – 2689-1026)
VOLUME 05 ISSUE 08 Pages: 77-81
SJIF IMPACT FACTOR (2020: 5. 286) (2021: 5. 64) (2022: 6. 319) (2023: 7. 396)
OCLC – 1121105510
Publisher: The USA Journals

in Women Who Have Not Progressed After First-Line Chemotherapy for Advanced Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (AEOC): Results of an International Intergroup Trial (AGO-OVAR 16) American Society of Clinical Oncology. – 2013. – T. 31.

8. Fountzilas E., Said R., Tsimberidou A. M. Expanded access to investigational drugs: balancing patient safety with potential therapeutic benefits //Expert opinion on investigational drugs. – 2018. – T. 27. – №. 2. – C. 155-162.
9. Green A. E., Rose P. G. Pegylated liposomal doxorubicin in ovarian cancer //International journal of nanomedicine. – 2006. – T. 1. – №. 3. – C. 229.
10. Lee A. T. J., Jones R. L., Huang P. H. Pazopanib in advanced soft tissue sarcomas //Signal transduction and targeted therapy. – 2019. – T. 4. – №. 1. – C. 16.
11. Oaknin A. et al. A phase II study of pazopanib in recurrent or persistent ovarian (EOC), peritoneal (PPC), or Fallopian tube cancer (FTC): A Spanish Ovarian Cancer Group (GEICO) study. – 2012.
12. Gulia S. et al. Pazopanib and oral cyclophosphamide in women with platinum-resistant or-refractory epithelial ovarian cancer //JCO Global Oncology. – 2020. – T. 6. – C. 542-547
13. Gupta S. et al. A phase II study of oral metronomic combination therapy in relapsed epithelial ovarian cancer. – 2013. Pandey A. et al. Outcomes of advanced epithelial ovarian cancer with integration of metronomic chemotherapy: An Indian rural cancer centre experience //South Asian Journal of Cancer. – 2016. – T. 5. – №. 02. – C. 059-062.
14. Perrone M. G. et al. Translational Theragnosis of Ovarian Cancer: where do we stand? //Current Medicinal Chemistry. – 2020. – T. 27. – №. 34. – C. 5675-5715
15. Saiyed M. M., Ong P. S., Chew L. Off-label drug use in oncology: a systematic review of literature //Journal of clinical pharmacy and therapeutics. – 2017. – T. 42. – №. 3. – C. 251-258
16. Saidkulov B. et al. Recurrent ovarian cancer: mechanisms of development of peritoneal malignant ascites //European Journal of Molecular and Clinical Medicine. – 2020. – T. 7. – №. 2. – C. 2423-2428.
17. 17. Zhang Y. et al. The Efficacy and Safety of Pazopanib Plus Chemotherapy in Treating Recurrent or Persistent Ovarian Cancer: A Systematic Review and Meta-Analysis //American Journal of Clinical Oncology. – 2023. – T. 46. – №. 6. – C. 25