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Research Article

Low Dose Taxol in Platinum-Resistant Recurrent Ovarian Cancer

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Abstract

Introduction: Epithelial Ovarian cancer is the third most commonly diagnosed gynecologic malignancy. With the highest mortality rate and worst prognosis among all gynecologic cancers. The Lifetime risk of developing ovarian cancer is 1.3%.

Aim: The study aims to critically analyse the weekly paclitaxel activity level in a patient population with platinum/paclitaxel-resistant ovarian cancer.

Methods: This is a single institutional retrospective study analysing patients' medical records with platinum-resistant recurrent epithelial ovarian cancer. This study analysed the single regimen – low dose paclitaxel 80 mg/m2 used weekly for 18 cycles. Patients were eligible if recurrence occurred less than six months from primary platinum-based treatment and received low-dose paclitaxel as a weekly regimen during the relapse. The outcomes analysed were survival benefits, ORR, and toxicities.

Results: 27 patients with recurrent platinum-resistant ovarian cancer who received low-dose paclitaxel chemotherapy were analysed. Demographic and clinical characteristics were studied. The period between the final platinum treatment and relapse ranged from 0.2 to 5.2 months, with a median of 2.7 months. The side effects were tolerable, and more than 60% of the patients received 18 cycles of chemotherapy. The complete response rate was 33%, and the partial response rate was 29%. The median PFS was 9.8 months.

Conclusion: Weekly paclitaxel regimen shows a good response in platinum resistance to ovarian cancer with improved quality of life and survival benefits with a reasonable toxicity profile.

Key words: Weekly chemotherapy, Dose-dense chemotherapy, Paclitaxel

INTRODUCTION

Epithelial Ovarian cancer is the third most commonly diagnosed gynecologic malignancy. With the highest mortality rate and worst prognosis among all gynecologic cancers. The Lifetime risk of developing ovarian cancer is 1.3%.[1] Epithelial ovarian cancer generally shows a very good response to platinum-based chemotherapy along with complete or optimal cytoreductive surgery. Nearly 70% of ovarian cancers repeatedly recur over time.

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According to the Ovarian Cancer Research Alliance (OCRA), the risk of EOC recurrence is approximately 10 % in stage 1,30 % in stage 2, 70 to 90 % in stage 3 and 90 to 95 % in stage 4. In total, about 70 % of patients with EOC experience a recurrence. In stage III disease-For patients with low residual disease (all lesions < 1 cm in size following surgical debulking), the risk for recurrence after completion of primary therapy is 60% to 70%; for women with large-volume residual disease, the risk is estimated at 80% to 85%. 25% of ROC occurs within six months after the end of primary chemotherapy and 75 – 80% after six months.[2] The mean 5-year survival rate following the diagnosis of recurrent EOC is < 10%.

The standard approach for treating recurrence is chemotherapy, and secondary cytoreduction is suitable only in the highly selected group. Most patients undergo many chemotherapy regimens, and deciding to select a regimen

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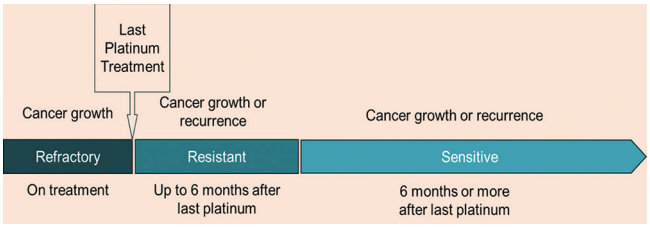
is a perplexing issue. Platinum sensitivity, residual toxicity, age, performance status, treatment-free interval, and the impact on quality of life due to the adverse effects of treatment should all be considered.

Patients with recurrent disease are grouped as *platinum-sensitive, partly sensitive*, or *platinum-resistant*. The platinum-resistant disease is defined as progression within six months of completing the primary platinum-based chemotherapy.



Patients with the refractory disease usually show evidence of poor response to front-line therapy, most often in the form of progressive disease. These patients exhibit poor objective responses to almost all agents available for re-treatment, and treatment choice depends upon patient wishes and comorbidities. Platinum resistance is observed in approximately 23% of patients. It poses a tough therapeutic challenge as they have a worse prognosis when compared with those who have a platinum-free interval of more than six months.

Few novel agents with unique cytotoxic mechanisms of action have been the most commonly utilized choices in the platinum-resistant setting. Combination therapies have shown less benefit than single-agent therapy in resistant/ refractory settings. The reported response rates are low, about 10% to 15%, and the Median time to progression is 3–4 months. The goal of chemotherapy is to palliate symptoms and improve quality of life. Chemotherapy options include Pegylated liposomal doxorubicin (PLD), Weekly Paclitaxel (80 mg/m^2), Gemcitabine, Topotecan, Etoposide.[3]

The study aims to critically analyse the level of activity of weekly paclitaxel in a patient population with platinum/ paclitaxel-resistant ovarian cancer and analyse the survival benefits, ORR, and toxicities. The primary endpoints were ORR and PFS. The secondary endpoints were OS, quality of life (QOL), and toxicities.

MATERIALS AND METHODS

This is a single institutional retrospective study. The medical records of patients with platinum refractory/ resistant recurrent epithelial ovarian cancer from 2015 to 2020 were analysed after being approved by the departmental review board of the institution. Patients were eligible if recurrence occurred less than six months from primary platinum-based treatment and received low-dose paclitaxel as a weekly regimen during the relapse.

A single regimen was analysed in this study – low-dose paclitaxel 80 mg/m^2 used as a weekly regimen for a total of 18 cycles. Clinical response in patients was analysed by factors such as improved performance status, reduction/ resolution of ascites and drug-related toxicities. Tumor response was retrospectively evaluated with RECIST[4] and GCIG[5] CA-125 criteria Outcomes analysed were ORR and PFS. PFS was measured from the date of first chemotherapy to the date of disease progression, death, or final follow-up.

The statistical analysis was performed using SPSS, version 2 and a p-value <0.05 was considered statistically significant. The mean and median were used for the description of the data. PFS was measured from the date of first chemotherapy to the date of disease progression, death, or final follow-up. ORR was calculated as the inclusion of both complete and partial response groups.

RESULTS

In total, 27 patients with recurrent platinum-resistant ovarian cancer who received low-dose paclitaxel chemotherapy in our hospital were analysed. Demographic and clinical characteristics are shown in Table 1. The mean age of the patients was 56 years. Most patients were diagnosed at an advanced stage (stage III or IV, 80%), with 81% histologically confirmed serous carcinoma.

The median duration of the platinum-free interval was 2.7 months, with a range of 0.2 to 5.2 months. The platinum refractory group had 14% of the patients, and the resistant group had the majority of 86% of patients [Table 1].

Almost 62% of the patients completed a total of 18 cycles. This non-completion of cycles was commonly due to practical difficulties in travel and financial issues and not due to toxicities, as the grade ¾ toxicity rate was very low. On average, the patient's performance status improved after

Table 1: Demographic and clinical characteristics of the patients

PARAMETERS	No.
Number of patients	27
Mean age (years)	56
Optimal cytoreduction at primary treatment	4 (14%)
Suboptimal cytoreduction at primary treatment	16 (59%)
Initial FIGO STAGE:	
I - II	12 (19%)
III - IV	49 (80%)
Primary Histology	
Serous	50 (81%)
Endometroid	5 (8%)
Clear cell	3 (4%)
Mucinous	3 (4%)
others	0
Platinum Free Interval	
Median	2.7 months
Range	0.2-5.2 months
< 1 month (refractory)	4 (14%)
1-6 months (resistant)	23 (86%)

Table 2: Outcome and chemotherapy response of the study

RESULTS	GC
No. of patients completed 18 cycles	17 (62%)
No. of patients with grade 3/4 toxicity	2 (<1%)
Improved performance status	18 (66%)
Reduction of ascites	20 (74%)
Chemotherapy response	
Complete response	9 (33%)
Partial response	8 (29%)
Stable disease	7 (25%)
Progressive disease	3 (11%)
Median PFS	9.8 months

3-4 cycles, reflecting improved appetite and sense of well-being. There was a drastic improvement in the control of ascites after the same 3-4 cycles. Complete resolution was ascites was noted in the majority, which indirectly improved the patient's performance status [Table 2].

In patients who completed all 18 cycles, Complete response to chemotherapy was observed in 33% of the patients, which is quite higher than the other single agent regimens used in other retrospective studies (Docetaxel – 22%, Gemcitabine – 19%, Oral etoposide – 27%). Partial response and stable disease was observed in 29% and 25%, respectively. Disease progression while on weekly paclitaxel was noted in 11% of patients, which could be explained due to tumor biology. PFS observed was 9.8 months which was not less than other single-agent regimes.

DISCUSSION

With the propensity of repeated recurrences, consideration of the quality of life is essential in decision-making about chemotherapy regimens in recurrent ovarian cancer. Dose-dense therapy is a strategy to enhance antitumor activity and prolong the survival of patients. The cumulative drug dose remains constant, but the same drug is administered over a shorter period. Increased dose density is achieved by reducing the interval between each dose of chemotherapy. Mathematical models of tumor growth have provided the basis for the clinical application of dose-dense chemotherapy. Based on Norton- Simon's hypothesis, the theoretical basis for this dose-dense chemotherapy strategy is derived from the Gompertzian model.[6] In the Gompertzian model, smaller tumors grow faster, so tumor regrowth between treatment cycles is more rapid when cell kill is greatest. The Norton–Simon model suggests that increasing the dose density of chemotherapy will increase efficacy by minimizing the opportunity for the regrowth of tumor cells between cycles of chemotherapy.

In tumor growth kinetics, the exponential phase of the tumor-growth curve has the highest proportion of tumor cells undergoing mitosis. It is here where tumor cells are most sensitive to the cytotoxic effects of paclitaxel. Paclitaxel inhibits mitosis in the late G2-M phase Dose-dense approach allows constant exposure of paclitaxel to this phase which in turn enhances antitumor activity from greater drug exposure. Weekly paclitaxel may have a direct anti-angiogenic effect compared to the 3-weekly regimen.[7] Acquired resistance to the cytotoxic effects of 3-weekly paclitaxel could be reversed by the weekly administration, which has better anti-angiogenic and vascular disruption effects.

Evaluation of response to dose-dense chemotherapy has been done in primary settings in various retrospective and prospective studies.[8] In JGOG 3016 trial, a prospective study of 632 Japanese populations by Katsumata *et al.* in 2013, better survival was observed in serous histology with a residual disease of >1cm in the primary setting.[9] This study was the only one to show a good response to the weekly paclitaxel regimen. The same regimen was critically analysed in a randomized controlled trial GOG262 by Chan *et al.* in 2016. Along with bevacizumab, weekly paclitaxel showed better PFS when given without bevacizumab.[10] In the MITO 7 trial, a low dose of 60mg/m^2 showed better quality of life without advantage in PFS.[11] The latest study by Andrew *et al.*- ICON8 in 2019 in 1566 patients with a predominantly European population failed to show survival benefits in primary settings.[12] The difference in outcomes of the studies mentioned above could be attributed to the pharmacogenomics difference between the study population analysed.

In the recurrent platinum setting, treatment options are limited, and decision-making of regimens is mainly based on improving the symptoms and thereby providing a

better quality of life. A phase III RCT by Mutch *et al*. in 2007, comparing PLD and gemcitabine, showed Similar efficacy & therapeutic index with different toxicity profiles. The PLD group showed significantly more HFS and mucositis. The gemcitabine group with significantly more constipation, nausea/vomiting, fatigue, and neutropenia (but not febrile neutropenia).

Weekly paclitaxel has shown a reasonable response rate in our study which is better than other single regimens. The dose-dense regimen's reduction in ascites was well observed, reflecting its anti-angiogenic effect. The toxicity profile is also better than the other regimens. The most commonly observed toxicity was anaemia. Sensory neuropathy and alopecia rates were similar to three weekly regimens. The main disadvantage of this regimen is treatment delays and omissions due to practical issues related to travel and repeated hospitalization for daycare chemotherapy.

Recent advances in the management of ovarian cancer include targeted therapy and immunotherapy. Many studies are evaluating different combinations of targeted therapy with chemotherapy, including weekly regimens. As most of the patients with the platinum-resistant disease are supposed to be BRCA negative, response to targeted therapy with PARP inhibitors is questionable in this particular group of patients.[13]

The platinum-resistant group has a high propensity for disease progression during treatment. So, the main aim of treatment is to control disease progression and provide a good quality of life with at least a reasonable maximum survival benefit.[14] Weekly paclitaxel is best suitable to low resource settings, providing all the above benefits at a reasonable cost, as observed in our study.

The main disadvantage of this study is the lack of comparative arms and retrospective analysis. A prospective randomized study of weekly paclitaxel in a platinum-resistant setting, along with comparable regimens including the recently targeted therapy drugs, would throw light on the better management of this group of patients in future.

CONCLUSION

A weekly paclitaxel regimen shows a good response in platinum resistance to ovarian cancer with improved quality of life and survival benefits with a reasonable toxicity profile.

DECLARATIONS

Ethical approval

None

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