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Original Research

Treatment Outcomes of Epithelial Ovarian Cancer A Longitudinal Study

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Objective: To evaluate the treatment outcomes in patients with epithelial ovarian cancer following neoadjuvant chemotherapy presenting at a tertiary care hospital.
Materials and methods: It was a longitudinal study conducted at the department of medical oncology, Jinnah postgraduate medical center, Karachi Pakistan from May 2018-Feb 2020. One twenty-five women of age 20-80 years with confirmed diagnosis of ovarian carcinoma (stage 1-4) who were referred from different medical institutes of Karachi were included in the study. Surgery and systematic chemotherapy were the primary treatment at the time of ovarian cancer diagnosis. Until death or last follow-up, treatment results were measured. Based on the treatments received from recurrence, systematic chemotherapy was further classified as 2nd line and 3rd line. Females who relapse after 6 months with platinum based treatment were underwent for re-treatment with carboplatin and cisplatin in combination or alone or those who recurred within 6 months and progress on 1st line were treated with non-platinum based systematic chemotherapy. SPSS version 23 was used to analyze data.
Results: The mean age of the study sample was reported as 46.23 years. The cumulative survival proportion of complete remission after first line platinum based chemotherapy with respect to duration of 1st line therapy was estimated as 0.027 and the median survival time was reported as 135 (95% CI: 128.81-141.18) days. The cumulative survival proportion of complete remission after second line chemotherapy with respect to duration of 2nd line therapy platinum based was estimated as 0.82 and the median survival time was reported as 156 (95% CI: 144.18-167.81) days. Hence, statistically significant difference was observed between platinum and non-platinum based chemotherapy (p=0.008) in second line therapy. Whereas, no case of complete remission occurred after third line chemotherapy.
Conclusion: The chemotherapy based on platinum (1st line) showed complete remission in most of the patients. After second line therapy, few patients showed disease progression and they underwent for third line therapy. The median time from 2nd line therapy to 3rd line therapy was reported as 123 days. In third line therapy, majority patients received non-platinum based chemotherapy where majority showed disease progression. The median survival time of 2 patients who died during third line therapy was reported as 8.75 months. The median survival time after 1st line therapy was 150 days. The median survival time after 2nd line therapy was 156 days.

Introduction

The carcinoma of ovaries is ranked as the 7th most common cause of mortality among other malignancies and is 6th most commonly occurring carcinoma among other cancers. However, it is more prevalent in Asian nation. In India, it is third leading cause of malignancy among women and 4th commonest carcinoma in Pakistan. Pakistan comprises of around eighteen million populations

with an immense weight of the illness. The age-related occurrences of ovarian malignant growth fluctuate somewhere in the range between 5.4 and 8.0 per hundred thousand individuals in various areas of the nation. Cancer of ovaries has the most noticeably poor outcomes among all gynecological malignancies. The general five-year survival is roughly forty five percent, fundamentally because of the late diagnosis [1-5]. Researches have shown that a combination of surgery along with post-chemotherapy has enhanced survival rates in women having advance stage carcinoma of ovaries than those who did not receive proper treatment [6].

The treatment and management of ovarian cancer has been upgraded in past few years. In the USA, cisplatin was used as chemotherapeutic agent. With the advances in the treatment options, the ideal treatment rates have been enhanced remarkably since past decade with an increase in survival rate as confirmed by the study conducted in Netherlands [7]. A recent investigation regarding ovarian cancer in the US has found that almost 50% of older-aged women had surgery followed by six cycles of chemotherapy [8]. In the early 70s, the idea of carrying out a cellular reduction surgery in order to remove cancer in ovaries followed my utilization of paclitaxel-containing chemotherapy in early 90s. A systemic review have shown great survival rates following debulking surgery [9]. The preliminaries inspected the advantages of chemotherapy for ovarian disease. They reasoned that platinum-based chemotherapy with blend of taxane can decrease the danger of ovarian malignant growth by 55% out of which, the 30% of the advantage may likewise be accomplished with a standard platinum-based blend. Surveys that condensed later clinical researches indicated likewise results [10, 11]. In light of evidences, the chemotherapy has been suggested in all women with ovarian malignancy following surgical reduction [12]. In the course of recent years, various investigations have archived that numerous chemotherapy specialists for ovarian carcinomas are financially practical in the preliminary setting [13-15].

The vast majority of the cancers of ovaries are treated by gynecologists due to shortage of gynecological oncologists. A large number of the patients receive way below treatment than standard treatment protocol due to financial and economical requirements. Numerous patients of Pakistan belong to rural areas with the lack of sources and poor access to particular human services. The restrictive expense of antineoplastic medications is a significant impediment for a significant number of the patients to proceed with the treatment. Late diagnosis, improper administration, and lack of interest to consistent treatment are all together accountable for lowering survival in the patients. There is a need to unbiasedly evaluate these components regarding ovarian carcinoma. Therefore, the current study determines the treatment pattern and their outcomes among ovarian cancer patients.

Materials and Methods

It was a longitudinal study conducted at the department of medical oncology, Jinnah postgraduate medical center (JPMC), Karachi Pakistan from June 2019 to March 2021. Sample size was estimated using open epi sample size calculator by taking statistic of mortality as 65% [16] for women with ovarian cancer who underwent neoadjuvant chemotherapy, margin of error as 8.5% and 95% confidence interval, the estimated sample size was 121≈125 patients. All women 0f 20-80 years with confirmed diagnosis of ovarian carcinoma (stage 1-4) from JPMC and who were referred from different medical institutes of Karachi were included in the study. Patient with history of platinum based agents and pregnant women were excluded from the study.

The ethical approval was sought out before initiation of study (NO.F.2-81-IRB/2019-GENL/7552/JPMC). The written informed consent was taken from all the eligible patients before data collection from patient or guardian. The details regarding socio-demographics, medical history, histological features, family history of breast cancer, family history of other cancer and clinicopathological characteristics were reported on predesigned proforma.

Surgery and systematic chemotherapy were the primary treatment at the time of ovarian cancer

diagnosis. Until death or last follow-up, treatment results were measured. Based on the treatments received from recurrence, systematic chemotherapy was further classified as 2nd line and 3rd line. All females who underwent 1st line chemotherapy based on platinum were assessed in terms of platinum free interval (PFI) for treatment response. PFI was defined as the number of months from the last platinum dose to recurrence. Females with PFI of 6 months or more were considered to be platinum-sensitive, females with PFI of less than 6 months were considered to be platinum-resistant disease and platinum-refractory disease if patients did not respond at least partially to 1st line platinum therapy. Platinum-based chemotherapy includes carbonplatin and paclitaxel in combination or separately. Females who relapse after 6 months of 1st line with platinum based treatment were underwent for re-treatment with carboplatin and cisplatin in combination or alone. Retreatment were not considered for the females who had history of adverse event, hypersensitivity reaction or persistent toxicities from 1st line chemotherapy.

SPSS version 23 was used to analyze data. Mean and SD were reported for normally distributed numeric variables whereas median and interquartile range were calculated for non-normally distributed numeric variables. Frequency and percentage were computed for categorical or nominal variables. P-value<=0.05 was considered as statistically significant. Kaplan Meier and time to event plot were used to investigate all patients who achieved complete remission after systematic chemotherapy with respect to duration of therapy. Log rank test was applied to compare the factor i.e. platinum based chemotherapy with probability of survival. P-value less and equal to 0.05 will be taken as statistically significant.

Results

The mean age of the study sample was reported as 46.23 years. Majority of the females belonged from rural area (63.2%), illiterate (54.4%), had monthly income 15,000-30,000 (51.2%), married (76%) and unemployed (97.6%). The females who were ever married, majority of them had more than 2 parity (74.4%). About 74.4% had vaginal delivery and only one female had menopause therapy. One hundred and fourteen patient had no excess obesity, 8.8% had positive family history of breast cancer whereas 6.4% had positive family history of other cancers and only 5 patients had use oral contraceptives (Table 1).

	Mean	SD
Age (years)	46.23	10.5
	n	%
Residence		
Rural area	79	63.2
Urban area	46	36.8
Education		
Illiterate	68	54.4
Primary	33	26.4
Matric	16	12.8
Intermediate	4	3.2
Graduate	4	3.2
Monthly income		
<15,000 rps	36	28.8
15,000-30,000 rps	64	51.2
>30,000 rps	25	20
Marital status		
Single	10	8
Married	95	76
Widow	13	10.4
Divorced	7	5.6

Occupation		
Employed	3	2.4
Unemployed	122	97.6
Parity		
<3	32	25.6
≥3	93	74.4
Mode of delivery		
C-section	32	25.6
Vaginal delivery	93	74.4
Menopause therapy		
Yes	1	0.8
No	124	99.2
Excess obesity		
Yes	11	8.8
No	114	91.2
Family history of breast cancer		
Yes	11	8.8
No	114	91.2
Family history of other cancer		
Yes	8	6.4
No	117	93.6
Oral contraceptive use		
Yes	5	4
No	120	96

Table 1. Baseline Characteristics.

About 67 patients had pathological stage 3 and 70 patients had clinical stage 3. All patients had epithelial ovarian cancer (100%). Median time since diagnosis of ovarian cancer was reported as 20.76 months and median CA125 level was reported as 828.00 U/ml. About 103 patients had no alternative therapy whereas 10 patients had hikmat as alternative therapy (Table 2).

	n	%
Pathological stage		
1	25	20
2	9	7.2
3	67	53.6
4	24	19.2
Clinical stage		
1	16	12.8
2	9	7.2
3	70	56
4	30	24
Alternative therapy		
No	103	82.4
Hikmat	10	8
Homeopathic	6	4.8
Spiritual healing	6	4.8
	Median	IQR
Duration of ovarian cancer since diagnosis (months)	20.76	12-23.16
CA125 (U/ml)	828	177.50-2000

Table 2. Clinicopathological Features of Females with Ovarian Cancer.

Figure 1 shows out of 125 patients with ovarian cancer, 8 patients had no surgery (6.4%), 10 patients were without hysterectomy (8%), 29 patients underwent standard surgery (23.2%) and 78 patients had debulky surgery (62.4%).

Figure 1. Treatment Pattern, Reasons for No Treatment, Treatment Response, Disease Progression and Survival.

One twenty-one patients underwent for first line chemotherapy and 4 patients didn't undergo for first line therapy because of patient decision (n=1) and death (n=3). Among patients who underwent for first line chemotherapy, 10 had no surgery (5.8%), 11 were without hysterectomy (8.7%), 17 had standard surgery (13.5%), 20 had primary interval debulky surgery (15.9%) and 68 had sub-optimal surgical staging (without lymph node dissection) (54%).

One twenty-two females who underwent for 1st line chemotherapy based on platinum. Among them 95% received doublet therapy and 5% received monotherapy. The mean duration of first line therapy was reported as 120.51±38.94 days ranging from 15 to 180 days. Treatment response was assessed in all the patients before and after six months and among them 20 had platinum-resistant disease, 69 were platinum-sensitive and 33 had platinum-refractory disease. After first line chemotherapy, 89 females showed complete remission, 19 females showed disease progression and 13 died. The median survival time of 16 patients who died during first line therapy was reported as 3 months (IQR: 2.07-6.75). About 45 platinum sensitive patients who relapse after 6 months of 1st line therapy with platinum based and 13 patients with platinum resistant and refractory disease underwent for second line therapy. The median time from 1st line therapy to 2nd line therapy was reported as 191 (IQR: 90.5-270) days for platinum sensitive. Among patients who received re-treatment with platinum based chemotherapy (n=27), 7 achieved complete remission, 17 had disease progression and 3 died. Among patients who received non-platinum based chemotherapy (n=31), 2 achieved complete remission, 26 had disease progression, 2 lost to follow-up and 1 died. The median survival time of 4 patients who died during second line therapy was reported as 14.25 months (IQR: 6.75-16.87). After second line therapy, 33 patients showed disease progression and among them 18 underwent for third line therapy. The median time from 2nd line therapy to 3rd line therapy was reported as 123 (IQR: 35-183.75) days. In third line therapy 3 patients received platinum based chemotherapy and 15 received non-platinum based chemotherapy. At the end of third line 14 patients showed disease progression, 2 lost to follow up and 2 died. The mean duration of third line therapy was reported as 90.66±44.86 days ranging from 24 to 210 days. The median survival time of 2 patients who died during third line therapy was reported as 8.75 months (IQR: 1.5-16.00).

The cumulative survival proportion of complete remission after first line platinum based chemotherapy with respect to duration of 1st line therapy was estimated as 0.027 and the median survival time was reported as 135 (95% CI: 128.81-141.18) days (Figure 2).

Figure 2. Probability of Complete Remission after 1st Line Chemotherapy.

About 7 events of complete remission occurred in second line platinum based chemotherapy whereas 2 events of complete remission occurred in second line non-platinum based chemotherapy. The cumulative survival proportion of complete remission after second line chemotherapy platinum based with respect to duration of 2nd line therapy was estimated as 0.38 and the median survival time was reported as 156 (95% CI: 144.18-167.81) days. Hence, statistically significant difference was observed between platinum and non-platinum based chemotherapy (p=0.008) (Figure 3).

Figure 3. Probability oF Complete Remission after 2nd Line Chemotherapy.

Lastly, no case of complete remission occurred after third line chemotherapy.

Discussion

This study delivers an exceptional viewpoint of treatment outcomes among ovarian cancer patients. The study suggests that ovarian cancer could occur in younger as well as older. The patients were also found to have positive family history of cancer and obesity was also linked to some extent. Few patients also used oral contraceptives and majority had more than three pregnancies along with more number of vaginal deliveries. The data also suggest that most of the patients belong to rural area and hence majority were not educated [17]. Carcinoma of ovaries usually occurs as progressive and extensive disease which appears to be significant reason of deaths [18]. This refutes with the findings of an Egyptian study where majority of the patients were diagnosed at early stage and 8% were having stage 3 cancer [19]. Considering the fact, present study results showed that about 53.6% and 56% patients had pathological and clinical stage 3 respectively similar to the study conducted in Asian region and western region also shows higher stage 3 involvement [20-22]. Voluminous studies had been conducted worldwide regarding the outcomes of platinum based therapy in ovarian cancer patients. The current study reveals that 13.5% patients had standard surgery whereas 54% patients had sub-optimal surgical staging (without lymph node dissection). The results are validated by Thrall et al. and Sehouli et al., where surgery was carried out in 58.8% and 89% respectively [23, 24].

A systemic review concluded that platinum based chemotherapy is beneficial in prolonging survival of the patients when used as adjuvant chemotherapy [25]. In a study, first line platinum based therapy was given in 63% patients. The survival from start of treatment until at the end of the treatment was 47 months [26]. Similarly, in the present study, 7.4% patients underwent for first line chemotherapy without surgery and survival rates were quite impressive. However, one study suggested that stage 1 and stage 2 ovarian cancers are not deemed to be chemotherapy treated as mortality rate was found 0.7 within 5 years [27]. The platinum based chemotherapy is also associated with no recurrence and increasing survival rates among patients of early stage ovarian cancer [28]. Similar results have been found out in another study [29]. The chemotherapy is associated with less risk of ovarian disease recurrence. In this way, chemotherapy in early stages ought to be considered in all patients. Another 5 years systemic review suggested that the platinum-based chemotherapy had better survivals by 7.1 times and survival was found increased without progression by 6.7 times [30].

Presently, chemotherapy as an adjuvant is suggested for patients at higher risk and patients with early stage incomplete staging. Though optimum regime is vacillating, majority of the specialists carry out combined treatment having paclitaxel and carboplatin as the efficiency has been found higher in previous studies and survival seems better in advance cases of ovarian cancer [31]. The present study results are in concurrence with few studies where platinum sensitive patients responded to platinum based chemotherapy in around 90% patients [32]. Another study also favors the use of platinum based chemotherapy. However, the drug regimen was different and main aim was to alleviate symptoms and improve quality of life in ovarian cancer patients [33].

In conclusion, the chemotherapy based on platinum showed complete remission in most of the patients. After second line therapy, few patients showed disease progression and they underwent for third line therapy. The median time from 2^{nd} line therapy to 3^{rd} line therapy was reported as 123 days. In third line therapy, majority patients received non-platinum based chemotherapy where majority showed disease progression. The median survival time of 2 patients who died during third line therapy was reported as 8.75 months. The median survival time after 1^{st} line therapy was 150 days. The median survival time after 2^{nd} line therapy was 156 days.

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Approval

The ethical approval was sought out before initiation of study (NO.F.2-81-IRB/2019-GENL/7552/JPMC)

Conflict of Interest

Non to declare

Ethical Declaration

The ethical issue was handled by institutional review board of JPMC.

Authors Contribution

All authors contributed equally.

Data Availability

Data is available from corresponding author on reasonable request.

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