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Original Research Article

Impact of the Treatment-Free Interval on Health-Related Quality of Life in Patients with Early-Stage Serous Epithelial Ovarian Cancer

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Abstract: ***Background:*** Although the incidence of ovarian cancer is less than that of other female cancers, the morbidity and mortality associated with the disease course is high. Because treatment involves radical surgery and intense courses of chemotherapy, health-related quality of life (HRQOL) is often compromised. Most patients recur post-first-line therapy and undergo multiple rounds of chemotherapy. Thus, HRQOL is further disrupted. ***Objective:*** The aim of this study is to assess impact of the treatment-free interval on health-related quality of life in patients with early-stage serous epithelial ovarian cancer. ***Methods:*** The cross-sectional observational study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total 38 women with histopathologically confirmed serous epithelial ovarian cancer were included in the study. Participants were divided into two groups according to their mutation status; patients with BRCA mutation were Exposed Group and those without BRCA mutation as Unexposed Group. The questionnaire was pretested, corrected and finalized. Data were collected by face-to-face interview and analyzed by appropriate computer based programmed software Statistical Package for the Social Sciences (SPSS), version 24. ***Results:*** In this study, maximum study subjects 26 (68.4%) were in >45 years age group and 12 (31.6%) were in ≤45 years age group. Mean age of the study subjects was 52.43±4.22 years and majority of the patients 29 (76.3%) were literate and 9 (23.7%) were illiterate. About 25 (65.8%) respondents had family history of breast / ovarian cancer and 11 (28.9%) had no family history of breast / ovarian cancer. Majority 20 (52.6%) respondents underwent Primary Debulking Surgery as primary treatment modality, whereas 18 (47.4%) did not receive Primary Debulking Surgery and majority respondents 21 (55.3%) received neoadjuvant chemotherapy and interval debulking surgery, whereas 19 (44.7%) respondents did not receive neoadjuvant chemotherapy and interval debulking surgery. About 8 (21.1%) respondents showed recurrence of disease and 30 (78.9%) respondents did not show recurrence of disease. In 8 respondents who had recurrence of disease, 5 (13.2%) respondents showed platinum sensitive recurrence and 3 (7.9%) respondents showed platinum resistant recurrence. Mean time of recurrence was 11.34±2.63 months, Mean progression free survival was 13.35±2.24 months and Mean treatment free interval (TFI) was 11.17±2.16 months respectively. About 35 (92.1%) respondents experienced fatigue, abdominal bloating in 24 (63.2%),

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pain in 32 (84.2%), peripheral neuropathy was in 14 (36.8%) respondents and sexual dysfunction in 5 (13.2%) respondents. ***Conclusion:*** In conclusion, women with epithelial ovarian cancer generally have satisfactory QoL in treatment-free interval. Family support could potentially provide a positive impact on QoL and would worth further research exploration.

Keywords: Ovarian Cancer, Chemotherapy, Treatment Free Interval, Overall Survival, Progression Free Survival, HRQOL.

INTRODUCTION

The eighth most frequent malignancy in women worldwide is ovarian cancer. It is representative of a diverse group of cancers with varying epidemiology, molecular biology, and pathologies. Histologically, 90% of ovarian tumors are categorized as epithelial malignancies. There is presently no reliable screening technique for epithelial ovarian malignancies, and early-stage symptoms are typically ambiguous and undetectable. Because of this, most patients receive an advanced diagnosis (International Federation of Gynecology and Obstetrics [FIGO] stages III–IV). According to GLOBOCAN 2018 and Torre *et al.*, 2018, these individuals typically have cancer that has progressed to distant organs (stage IV) or the abdominal cavity (stage III), which results in considerable morbidity and a high death rate [1, 2].

The 5-year overall survival rate for ovarian cancer is 45% on average in Nordic countries [3]. In the last 25 years, OS has not risen, despite all efforts being made to optimize the treatments [4]. Patients with ovarian cancer frequently get successive lines of chemotherapy during their treatment since the disease is chronic [5].

It has been demonstrated that PFS declines with each additional chemotherapy line in a number of advanced malignancies [6]. TFIs could be an additional tool for evaluating patient well-being and disease progression. TFI is the interval of time between the conclusion of one regimen and the start of the subsequent one.

It explains the period of time people spend off of actively treating cancer. Since previous chemotherapy lines affect the chance of response to other therapies, the number of prior chemotherapy lines is frequently a criterion for enrollment in clinical trials [7]. Still, the majority of research focuses on patients receiving chemotherapy as a second or third option. Research outside of third-line situations is required. As a result, we assessed the OS, PFS, and TFI rates for patients who were receiving more intensive care.

There are few studies where TFI has been used to assess the effectiveness of several chemotherapy lines for patients with ovarian cancer over the course of their whole follow-up [5] [8]. According to The National Quality Forum's guidelines, we have recently revealed our experience showing that most patients receive aggressive care in the final 30 days of their life [9]. In this study, we investigated the relationship between TFI and aggressive end-of-life care.

Treatment for epithelial ovarian cancer has traditionally consisted of combination chemotherapy after primary debulking surgery. Surgery's objectives are to remove visible tumors (debulking), get tissue for diagnostic confirmation, and assess the degree of the disease (staging) [10, 11, 12]. Long open vertical abdominal incisions are used for the surgical operations, which are usually rather thorough and involve complete removal of the uterus, all visible intraabdominal tumors, and ovarian tumors in addition to omental resection, lymph node sampling, and peritoneal/mesenteric surface biopsies. Thus, it is sometimes difficult to prevent intra- or postoperative problems, which may have long-term repercussions on quality of life (QoL). Patients with stage II–IV disorders should always get systemic chemotherapy, either prior to or following surgery. In certain situations, chemotherapeutic drug regimens comprising two or more are typically recommended [13, 14]. Chemotherapy side effects are well-documented, consistent, and often quite serious. Long-term QoL may be further negatively impacted by this. Women with epithelial ovarian cancer may experience long-term illness and treatment-related morbidities that have a substantial impact on quality of life, even though survival rates vary mostly according on stage.

Numerous aspects of quality of life, such as physical, functional, mental, and sociological, have been negatively impacted by epithelial ovarian cancer in the past [15]. Nevertheless, the majority of the subjects in these trials were older female patients. However, these studies focused mainly on women with advanced disease. There has been very limited information regarding QoL of women who have the early disease in comparison to those with more advanced disease especially in the context of Asian culture.

METHODOLOGY

The cross-sectional observational study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical

University (BSMMU), Dhaka. A total 38 women with histopathologically confirmed serous epithelial ovarian cancer were included in the study. Participants were divided into two groups according to their mutation status; patients with BRCA mutation were Exposed Group and those without BRCA mutation as Unexposed Group. Patients who matched the inclusion and exclusion criteria were approached for participation in the study. Patients who were not willing to give consent were excluded. Purposive sampling was done according to the availability of the patients who fulfilled the selection criteria. Face to face interview was done to collect data with a semi-structured questionnaire. After collection, the data were checked and cleaned, followed by editing, compiling, coding, and categorizing according to the objectives and variable to detect errors and to maintain consistency, relevancy and quality control. Statistical evaluation of the results used to be obtained via the use of a window-based computer software program devised with Statistical Packages for Social Sciences (SPSS-24).

RESULT

Table I: Distribution of the patients according to age (n = 38)

Age (years)	Frequency	%
≤45	12	31.6
>45	26	68.4
Mean ± SD: 52.43±4.22		

Table I shows that, maximum study subjects 26 (68.4%) were in >45 years age group and 12 (31.6%) were in ≤45 years age group. Mean age of the study subjects was 52.43±4.22 years.

Table II: Distribution of the patients according to educational status (n = 38)

Education	Frequency	%
Illiterate	9	23.7
Literate	29	76.3

Table II shows that, majority of the patients 29 (76.3%) were literate and 9 (23.7%) were illiterate

Table III: Distribution of the patients according to family history of breast / ovarian cancer (n = 38)

Family history of breast / ovarian cancer	Frequency	%
Yes	11	28.9
No	25	65.8

Table III shows that, 25 (65.8%) respondents had family history of breast / ovarian cancer and 11 (28.9%) had no family history of breast / ovarian cancer

Table IV: Distribution of the patients according to Primary Debulking Surgery (n = 38)

Primary Debulking Surgery	Frequency	%
Yes	20	52.6
No	18	47.4

Table IV shows that, majority 20 (52.6%) respondents underwent Primary Debulking Surgery as primary treatment modality, whereas 18 (47.4%) did not receive Primary Debulking Surgery

Table V: Distribution of the patients according to Neoadjuvant Chemotherapy and Interval Debulking Surgery (n = 38)

Neoadjuvant Chemotherapy and Interval Debulking Surgery	Frequency	%
Yes	21	55.3
No	19	44.7

Table V shows that, majority respondents 21 (55.3%) received neoadjuvant chemotherapy and interval debulking surgery, whereas 19 (44.7%) respondents did not receive neoadjuvant chemotherapy and interval debulking surgery

Table VI: Distribution of the patients according to status of recurrence of disease after treatment (n = 38)

Status of recurrence	Frequency	%
Yes	8	21.1
No	30	78.9

Table VI shows that, 8 (21.1%) respondents showed recurrence of disease and 30 (78.9%) respondents did not show recurrence of disease

Table VIII: Distribution of the patients according to types of recurrence (n = 38)

Types of recurrence	Frequency	%
Platinum Sensitive	5	13.2
Platinum Resistant	3	7.9
No	30	78.9

Table VIII shows that, in 8 respondents who had recurrence of disease, 5 (13.2%) respondents showed platinum sensitive recurrence and 3 (7.9%) respondents showed platinum resistant recurrence

Table IX: Distribution of the patients according to Time of recurrence, Progression free survival and Treatment free interval (n = 38)

Variables	Mean ± SD
Time of recurrence (months)	11.34±2.63
Progression free survival (months)	13.35±2.24
Treatment free interval (months)	11.17±2.16

Table IX shows that, Mean time of recurrence was 11.34±2.63 months, Mean progression free survival was 13.35±2.24 months and Mean treatment free interval (TFI) was 11.17±2.16 months respectively.

Table X: Distribution of the patients according to health-related quality of life (n = 38)

Health related complications	Frequency	%
Fatigue	35	92.1
Abdominal Bloating	24	63.2
Pain	32	84.2
Peripheral neuropathy	14	36.8
Sexual dysfunction	5	13.2

Table X shows that, 35 (92.1%) respondents experienced fatigue, abdominal bloating in 24 (63.2%), pain in 32 (84.2%), peripheral neuropathy was in 14 (36.8%) respondents and sexual dysfunction in 5 (13.2%) respondents

DISCUSSION

One of the most prevalent forms of cancer in women is ovarian cancer, which also happens to be the leading cause of death from gynecological cancer and one of the most common causes of deadly cancer in women overall. Most patients come with advanced-stage disease since the symptoms are generally ambiguous, making early detection difficult. Surgery and chemotherapy are typically used in the treatment of ovarian cancer. The first TFI was associated with better HRQL compared to other treatment phases, and that longer TFIs were largely associated with better HRQL. Gaining a better understanding of the relationship between HRQL and the first TFI could provide information for potential HRQL endpoints in randomized controlled trials [16], be a valuable aid to cost-effectiveness analyses and help inform clinical practice. In clinical practice, some treatments are used until disease progression, while others are used for a set number of cycles allowing patients to benefit from a TFI prior to relapse. A TFI resulting in an improvement in HRQL may be an important treatment benefit for patients.

The cross-sectional observational study was conducted in the Department of Gynecological Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. A total 38 women with histopathologically confirmed serous epithelial ovarian cancer were included in the study.

In this study, maximum study subjects 26 (68.4%) were in >45 years age group and 12 (31.6%) were in ≤45 years age group. Mean age of the study subjects was 52.43±4.22 years and majority of the patients 29 (76.3%) were literate and 9 (23.7%) were illiterate. About 25 (65.8%) respondents had family history of breast / ovarian cancer and 11 (28.9%) had no family history of breast / ovarian cancer. Majority 20 (52.6%) respondents underwent Primary Debulking Surgery as primary treatment modality, whereas 18 (47.4%) did not receive Primary Debulking Surgery and majority respondents 21 (55.3%) received neoadjuvant chemotherapy and interval debulking surgery, whereas 19 (44.7%) respondents did not receive neoadjuvant chemotherapy and interval debulking surgery. In another study most of the patients (80%, n = 151) had stage III or IV disease at the time of diagnosis. A majority of them (85%, n = 160) had underwent primary or secondary cytoreductive surgery [17].

About 8 (21.1%) respondents showed recurrence of disease and 30 (78.9%) respondents did not

show recurrence of disease. In 8 respondents who had recurrence of disease, 5 (13.2%) respondents showed platinum sensitive recurrence and 3 (7.9%) respondents showed platinum resistant recurrence. When all patients were included in analyses, the median number of the received chemotherapy lines was two (mean 3, range 1 - 14). Of the patients, 38% (n = 72) had received four or more lines of chemotherapy at the end of follow up. Each patient received a platinum-based regimen as the first-line regimen.

In subsequent treatment lines, the distribution of chemotherapy regimens was more diverse. Mean time of recurrence was 11.34±2.63 months, Mean progression free survival was 13.35±2.24 months and Mean treatment free interval (TFI) was 11.17±2.16 months respectively. About 35 (92.1%) respondents experienced fatigue, abdominal bloating in 24 (63.2%), pain in 32 (84.2%), peripheral neuropathy was in 14 (36.8%) respondents and sexual dysfunction in 5 (13.2%) respondents. As shown in another study, TFIs shortened significantly after the first relapse and subsequent number of chemotherapy lines ($p < 0.001$). After the first, second, third, fourth and 5+ chemotherapy lines median TFI was 12.0 (95% CI 9.2 - 14.8), 4.0 (95% CI 2.2 - 5.8), 3.0 (95% CI 1.4 - 4.6), 3.0 (95% CI 1.8 - 4.2) and 1.0 (95% CI 0.4 - 1.6) months, respectively [17]. The differences in TFIs were also seen when comparing platinum sensitive, semi-sensitive and platinum resistant patients. After the first, second, third, fourth and 5+ chemotherapy lines median TFI in platinum sensitive patients was 32 (95% CI 22.9 - 41.1), 11 (95% CI5.7 - 16.3), 4 (95% CI 0.0 - 11.2), 6 (95% CI 2.5 - 9.5) and 3 (95% CI 0.1 - 5.9) months respectively, ($p < 0.001$). In semi-sensitive patients median TFI was 8 (95% CI 6.4 - 9.6), 3 (95% CI 1.2 - 4.8), 6 (95% CI 2.3 - 9.7), 6 (95% CI 3.3 - 8.8) and 1 (95% CI 0.0 - 2.4) months respectively ($p < 0.001$) and in platinum resistant patients median TFI was 4 (95% CI 2.8 - 5.2), 3 (95% CI 1.5 - 4.5), 2 (95% CI 0.7- 3.3), 2 (95% CI 1.1 - 2.9) and 1 (95% CI 0.0 - 2.0) months respectively ($p = 0.003$) [17].

In another study showed that TFIs were significantly shortened after the first relapse when subsequent chemotherapy lines were used. Aggressive care at the end of life was associated with the decreased total treatment free time during the follow-up. Standards for the first line platinum-based chemotherapy regimens in ovarian cancer are well-established [18]. For very platinum sensitive patients a combination of carboplatin and pegylated liposomal doxorubisin is recommended [19].

However, in later relapses the best and the most effective regimens for the patient are not so clear. Patients in our cohort were treated according to recommendations since each patient received platinum in first line. The second line regimens were platinum-based when the patient was platinum sensitive and in platinum resistant situations pegylated liposomal doxorubicin was used most often. Generally, single antineoplastic agent is referred in patients with platinum resistant disease and poor prognosis. The main goal of the treatment in those patients is preservation of quality of life and avoid toxicities as much as possible.

As mentioned before, there is an unmet need for trials of patients that have received multiple chemotherapy lines [5]. Apart from BRCA status [20], there are no reliable predictors to help selection of the patients who are more likely to respond to three or more lines of chemotherapy. To identify those patients Hoskins *et al.,* [21] describe a model that predicts lack of benefit by the length of an interval between two preceding relapses, in which under 12 months from diagnosis to second relapse, under six months from first to third relapse and second to fourth relapse predict a survival of six months or less. A study by Hanker *et al.,* based on three clinical ovarian cancer clinical trials [22] showed that a maximum of three lines of subsequent relapse treatment seems to be beneficial according to OS for patients with recurrent ovarian cancer. Recently, a large GCIG Symptom Benefit Study reported that baseline HRQL (health-related quality of life) combined with clinicopathological prognostic factors like physical, cognitive and social functions and abdominal/GI symptoms is able to assist clinician in decision making of further cancer treatments [23].

When evaluating the effectiveness of non-curative treatments, OS is not only parameter of describing benefit. TFI is traditionally used to divide patients whether they are platinum sensitive or resistant [9]. In this study, we used TFI to describe the time when patients are without cancer-targeted treatment during their follow- up after serial chemotherapy lines. The correlation between longer TFI and better health-related quality of life has been reported in the treatment of multiple myeloma [15]. In ovarian cancer, TFIs has been shown to decrease significantly after serial chemotherapy treatments [3] and that was also noticed by us. In another study showed that, TFI was one month or less after the fifth relapse suggesting that by that time point at the latest further chemotherapy might be rather harmful than beneficial to patients [24].

When comparing platinum sensitive, semi-sensitive and platinum resistant patients we expectedly saw that TFIs after the first and second treatment line in platinum sensitive patients were notably higher, than in platinum resistant and semi-sensitive patients. Patients that experienced platinum resistant disease after the first relapse had very poor prognosis in general. According to TFIs, chemotherapies should be avoided after second-line treatments in those patients since TFIs were only two months or less [24].

Patients that received at least one form of aggressive care in the last 30 days of life had decreased overall TFI compared to those without aggressive care.

More specifically, patients without aggressive care at the end of life were more than half of their follow up time without cancer targeted medication compared to those patients with aggressive care and 41% of the follow up time without chemotherapies. In many cases the aim of chemotherapy is to palliate symptoms. In a study by Friedlander *et al.*, [25] in patients with recurrent ovarian cancer and palliative chemotherapy, half of the patients gained improvement regarding their symptoms, but many progressed rapidly. Thus, measures to document symptoms, adverse events and quality of life might be useful when deciding to further continue chemotherapy in recurrent settings.

CONCLUSION

In conclusion, several chemotherapy lines are frequently used in the treatment of individuals with ovarian cancer. After the initial relapse, TFIs get shorter; individuals who are platinum resistant in particular have noticeably shorter TFIs. Women with epithelial ovarian cancer generally have satisfactory QoL in treatment-free interval. Family support could potentially provide a positive impact on QoL and would worth further research exploration.

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