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Research Article

Response Rates of Second Line Chemotherapy Platinum Resistant Ovarian Cancer in Sudan: 2013-2017

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Abstract

Background: Ovarian carcinoma is the fifth leading cause of cancer death worldwide. The tumour mostly associated with various factors such as advanced age, early menstruation and gene association. We aimed to highlight the effectiveness of second-line chemotherapy in the management of ovarian cancer patients in Sudan.

Methods: The data collected from the hospital patients' records for five years period of time, including 62 patients with ovarian cancer who were treated by the second line platinum-resistant chemotherapy.

Result: The peak prevalence of the disease was found in Al-Jazeera state while the least in Al-Gadarif state. Age group above 55 years was the most affected group. The vast majority of patients showed partially reduction in mass's size. Others had complete disappearing of the mass or continuing of the tumor growth. All patients received a variant number of cycles of chemotherapy 3, 6, 2, 4, 5, 1 cycle respectively. 79.4% of the patients had achieved the normal value of cancer antigen 125 (CA125) levels after the treatment. In 50% of patients, cancer recurred after 1-2 months, 32.2% after 3-4 months and 17.8% after 5-6 months. The serous adenocarcinoma was found to be the most histological type whereas the least two types observed were clear cell carcinoma and serous papillary adenocarcinoma.

Conclusion: Our findings suggested that, Al-Jazeera state citizens were more vulnerable to resist first-line chemotherapy than others. The Sudanese patients with ovarian cancer may have a better response to Gemzar but further studies are needed to confirm this result.

Keywords: Adenocarcinoma; Gemzar; Ovarian Cancer; Second Line Chemotherapy, Sudanese Patients

Abbreviation

CA125: Cancer Antigen 125; CT: Computer Imaging; EOC: Epithelial Ovarian Cancer; FMOH: Federal Ministry of Health; IV: Intravenous; RICK: Radiation and Isotopes Centre Khartoum; WHO: World Health Organization.

Background

Ovarian cancer is one of the most widely distributed malignancies worldwide and is considered as the lethal gynaecological type and the fifth leading cause of cancer death [1-4], due to high recurrence rate which is resisting to the chemotherapy [5]. Nearly, 3 out of 4 of epithelial ovarian cancer (EOC) types present with late advanced stage [6]. The lifetime risk of developing ovarian cancer in the general population is 1.4 per cent and the mean age of presentation is 64 years, even though the incidences are varied by regions [7]. Many factors play a major role in disease development including advance age, genetics associations, early menstruation [8], late menopause and hormonal therapy Ovarian tumors are mainly primary, but secondary tumors from the colon [9], stomach, small intestine, pancreas [6], breast and even thyroid cancer [10] are also common. Based on the histological principles, the world health organization (WHO) classified ovarian cancer into many types [11]. The high grade serous ovarian carcinoma is the most common type [12]. The current management of ovarian tumours at an early stage is surgical removal, followed by a combination platinum/taxane chemotherapy [13,14]. While conventional therapy is considered for patients who presented with advanced late stage [15]. 60% of them will have disease recurrence, and up to 90% will die eventually [6]. The survival rate in early stage approaches 90%, however most of the ovarian tumours diagnosed in their advanced stage [16]. Ovarian tumours can arise from any of three potential sites: fallopian tube, mesothelium lined peritoneal cavity and the ovary surfaces [17]. The risk of metastasis of ovarian cancer depends on the stage and histological subtype of the tumour [18]. Women with ovarian cancer have a good response to standard platinum treatment, although the majority of patients presented at the late stage will ultimately relapse [19], and resist the first line treatment. Platinum resistant ovarian cancer is defined as disease recurrence within 6 months after completion of first-line platinum-based chemotherapy and when cancer shows growth during treatment or no evidence of tumour regression after 4-6 cycles of platinum treatment [20]. Recently, platinum resistance has included many chemotherapeutic agents [5,21].

The decision of considering second-line chemotherapy in treatment of recurrent ovarian cancer is not yet fully clear with absence of standard chemotherapy against recurrent ovarian cancer or the platinum-resistant cancer [5,22]. Recent studies illustrate the genetic and epigenetic alterations in ovarian cancer such as changes in BRCA1 and 2, TP53, RB1, NF1, MYC and PTEN which play a major role in pathogenesis of the disease and hence can be considered as base for molecular targeted therapy. Furthermore, other study illustrates specific molecular changes in exact types of ovarian cancer [23,24]. Knowledge about early molecular changes in tumorigenesis can help in early detection and prevention of the disease [25]. In general Sudan has low data in regard to cancer only a few studies done for other types such as thyroid cancer [26,27], in contrast to ovarian cancer where are little information about the chemotherapy treatment of ovarian cancer, Therefore we are aiming to determine the effectiveness of second-line chemotherapy in the treatment of recurrent ovarian cancer in Sudan, determine the most effective type of second-line chemotherapy, the most common histological types and most common sites of metastasis.

Methods

This is a retrospective cross-sectional hospital based study which carried out at The Radiation and Isotopes Centre Khartoum (RICK) in Khartoum - Sudan. The study conducted between the periods of 2013-2017 for a number of 62 recurrent ovarian cancer patients. The data were selected based on specific criteria included only the patients who treated with the second-line chemotherapy platinum resistance and platinum-refractory. The designated questionnaire contains information that confirms cancer diagnosis by a clinical oncologist including patient's age, clinical presenting features, occupation, geographical and ethnic distributions, histopathological reports of ovarian cancer type, computerized tomography (CT) scan findings, CA 125value before and after treatment, the time interval between full course treatment and cancer recurrence and number of chemotherapy cycles received by the patients. The patients received multiple agents of second-line chemotherapy such as Gemzar in a dosage of 1 gram every 7 days for 3 times then repeated every 3 weeks, carboplatin in a dosage of 30 mg/m^2 every 4 weeks for 3-6 cycles, Docetaxel 60-75mg/m^2 intravenous (IV) administration over 1 hour followed by carboplatin AUC 5-6 mg.min/ml IV over 1 hour repeated every 3 weeks for 6 cycles. The ethical approval and formal consent were obtained from all patients, the federal ministry of health (FMOH) and the ethical committee of the RICK for scientific purposes.

Statistical analysis

Statistical software package SPSS version 17.0 used for data analysis. Percentages, frequency, valid per cent and cumulative per cent were calculated. The one-way analysis of variance (ANOVA) was used to calculate P- value for statistical significance and a value of $P< 0.05$ was considered as statistically significant, The Cox regression for the age of the patients, type of the chemotherapy, duration of treatment, Number of the treatment cycle, metastatic site and the response of treatment was significant (Table 1).

Omnibus Tests of Model Coefficient[a]									
-2 Log Likelihood	Overall (score)			Change from Previous Step			Change from Previous Block		
	Chi-square	df	Sig.	Chi-square	df	Sig.	Chi-square	df	Sig.
40.191	12.043	2	.002	13.333	2	.001	13.333	2	.001
a. Beginning Block Number 1. Method = Enter									

Table 1: Represent the cox regression of the age of the patients, type of the chemotherapy, duration of treatment, number of chemotherapy cycles, metastatic site and the treatment response.

Results

Gemcitabine (Gemzar) found to be the most widely used chemotherapeutic agent among studied patients (72.6%), followed by Gemzar nevalbin (8.1%), Gemzar cyclophosphamide (8.1%), both Taxol and carboplatin (6.5%), Gemzar oxaliplatin (3.2%) and finally Docetaxel (1.6%) as shown in (Table 2). All patients received various numbers of cycles of chemotherapy, about 40.3% of all patients received 3 cycles of chemotherapy. Patients who received 5 cycles and 1 cycle have fewest percentages among all patients of only 6.4% each. The rest received different number of cycles of chemotherapy as follow: 21% of patients received 6 cycles, 17.7% received 2 cycles and only 14.5% of the patients received 4 cycles (Table 2). The most common ovarian metastatic site distinguished before initiation of the second line platinum resistance chemotherapy was the pelvis (43.5%). Other metastatic sites and presentations were abdominal ascites (24.2%), combined ascites and pelvic mass (16.1%), both pelvic and liver metastasis with equal per cent (4.9%), liver metastasis with ascites (3.2%) each, pelvic and peritoneal metastasis (3.2%), isolated lung metastasis (3.2%) and lastly ascites with pelvic and lung metastasis together (1%) as mentioned in (Table 2).

Variable	Specific variable	Number of patients	Percentage	P-value
Histopathology type of ovarian cancer	Serous cyst adenocarcinoma	56	90.3%	<0.05
	Mucinous adenocarcinoma	2	3.2%	
	Transitional cell adenocarcinoma	1	1.6%	
	Endometrial adenocarcinoma	1	1.6%	
	Serous papillary adenocarcinoma	1	1.6%	
	Clear cell carcinoma	1	1.6%	
Site of Metastasis on CT scan before receiving second line chemotherapy	Pelvic mass	27	43.5%	
	Lung metastasis	2	3.2%	
	Ascites	15	24.2%	
	Pelvic mass and liver metastasis	3	4.9%	<0.05
	Pelvic mass and peritoneal metastasis	2	3.2%	
	Pelvic mass and Ascites	10	16.1%	
	Liver metastasis and Ascites	2	3.2%	
	Pelvic mass, lung metastasis and Ascites	1	1.6%	
Second line chemotherapeutic agent used	Gemzar	45	72.6%	
	Taxol and carboplatin	4	6.5%	
	Docetaxel	1	1.6%	<0.05
	Gemzar nevalbin	5	8.1%	
	Gemzar oxaliplatin	2	3.2%	
	Gemzar cyclophosphamide	5	8.1%	
Number of cycles received by the patient	1	2	3.2%	
	2	11	17.7%	<0.05
	3	25	40.3%	
	4	9	14.5%	
	5	2	3.2%	
	6	13	21%	

Table 2: Distribution of patients in the study according to the histological type of ovarian cancer, site of metastasis on CT scan, second line chemotherapeutic agent used and number of cycles received (total n= 62).

Regarding the effectiveness of chemotherapeutic agents, 42.2% of patients who have been treated with Gemzar showed zero mass in the CT abdomen report while 46.7% had partial decrease in mass's size and 11.1% experienced a continuous increase in the size of the tumor (Table 3). The most common histopathological type isolated from the patients was serous cyst adenocarcinoma in 90.3% of all patients, followed by mucinous adenocarcinoma (3.2%) and the remaining types in equal per cent of 1.6%, specifically transitional cell adenocarcinoma, endometrial adenocarcinoma, serous papillary adenocarcinoma and clear cell carcinoma (Table 2).

Concerning the tumor marker CA 125, 24.1% of patients had constant values before and after treatment. About 25.8% returned to the normal value, while 1.6% of the patients showed an increase in the levels of CA125. The rest of the patients did not achieve the normal levels of CA125. Overall, 79.4% of patients who received the second-line chemotherapy reached the normal range of 0-34 U/mL. Regarding the age groups, 37.1% of the patients were above 55 years old (Figure 1). We also observed that both Aljazeera and Khartoum state had the highest incidence of platinum resistant ovarian cancer by a value of 19% each (Figure 2), followed by

Chemotherapeutic agent	Complete response (zero mass size)	Partial response (decrease mass size)	Failure of treatment (increase mass size)	Total
Gemzar	19 (42.2%)	21 (46.7%)	5 (11.1%)	45 (100%)
Taxol and carboplatin	0 (0.00%)	4 (100%)	0 (0.00%)	4 (100%)
Docetaxol	0 (0.00%)	1 (100%)	0 (0.00%)	1 (100%)
Gemzar and nevalbin	0 (0.00%)	3 (60%)	2 (40%)	5 (100%)
Gemazr and oxaliplatin	0 (0.00%)	1 (50%)	1 (50%)	2 (100%)
Gemazr and cyclophosphamide	0 (0.00%)	4 (80%)	1 (20%)	5 (100%)
Total	19 (30.6%)	34 (54.8%)	9 (14.5%)	62 (100%)

Table 3: Shows distribution of patients according to their response to second line chemotherapeutic agents based on the change in size of the tumour on CT scan.

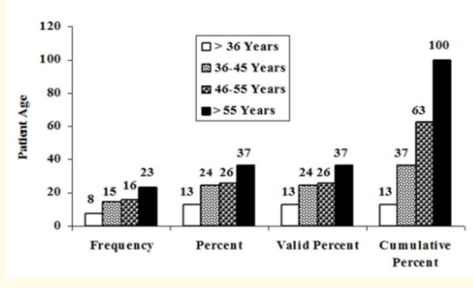

Figure 1: Demonstrates the distribution of platinum-resistant ovarian cancer patients according to their age, P-value (<0.01).

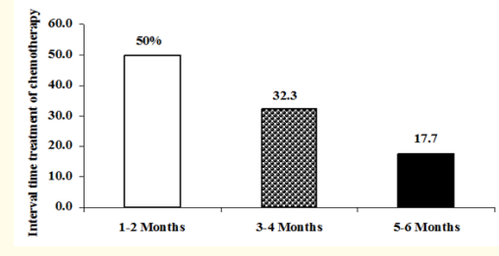

Figure 3: The figure represents the distribution of patients based on the duration between completion of the second line platinum resistance chemotherapy course and the disease recurrence.

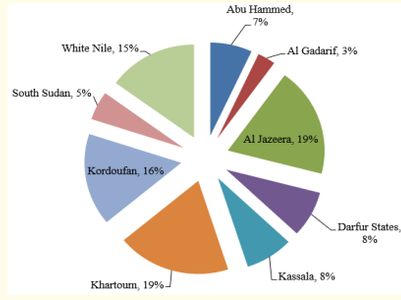

Figure 2: Illustrates the geographical distribution of platinum-resistant ovarian cancer patients in Sudan.

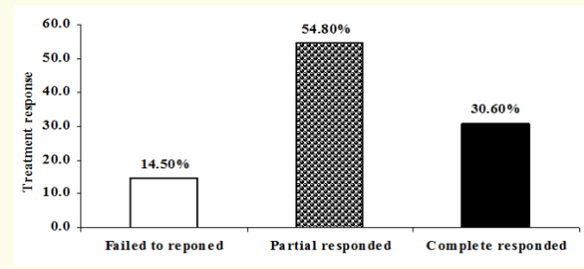

Figure 4: The graph presents a distribution of patients according to the response to second line platinum resistance chemotherapy.

Discussion

Many factors can contribute to the etiology of ovarian tumors, and these may include genetic mutation such as Breast Cancer (BRCA) mutation, postmenopausal stage, talcum powder [28] and hormonal changes in advance age [29]. Generally, this type of cancer is considered to be one of the most devastating cancer due to the lack of specific clinical symptoms before spreading beyond the level of the primary site and becomes difficult to treat [29]. The current study evaluated platinum resistance ovarian cancer patients using data obtained from a period of four years. The study showed that the age group above 55 years represent more than one-third of the patients. Our results are similar to earlier studies which reported that malignant ovarian cancer commonly observed in women ages 50-60 years [5,30-32]. Other reports revealed that the age group above 65 years constitutes 30-40% of all ovarian cancer patients [12,33]. This higher prevalence of age linked ovarian malignancy might be related to the factors of menopause and advanced age [29].

Here we reported for the first time that both Al Jazeera and Khartoum states had the same incidence of 19%. But taking into account the difference in population density between the two states, the prevalence was higher in Al Jazeera state compared to Khartoum state (2:1) [30]. The second line platinum resistance chemotherapy includes many types of treatment such as liposomal pegylated doxorubicin, topotecan, paclitaxel, oral etoposide and gemcitabine [30]. All of these chemotherapeutic agents have a similar response treatment rate of about 10% [5]. Our findings showed that the Gemzar had a better response comparing to the other used chemotherapeutic agents with 42.2% of the patients developed complete response. In addition, Gemzar treatment resulted in a partial response in 46.7% with shrinkage of the tumor's size. But the remaining 11.1% of the patients resisted the treatment. Our findings mismatch with the previous study that reported less effectiveness of Gemzar in ovarian cancer patients, as only 18.5% of cases showed a complete response, 29.6% had a partial response and 51.9% showed disease progression [12]. This could be due to the antitumor activity and higher tolerability against toxicity [33,34].

The serous cyst adenocarcinoma is the most common isolated histological type which had been identified in 90.3% of our studied patients. Our results are in agreement with those reported from other studies which showed the same isolated histological type [12,29,35-37]. This may be related to presence of significant number of genetically abnormal copies in adenocarcinoma type and absence of BRCA function [38]. The pelvic was the most common site of metastasis of ovarian cancer in our patients. This related to the fact that ovarian tumors tends to spread more easily by a passive mechanism through peritoneal fluids to the peritoneum and omentum [39]. As well as pelvic and para-aortaic lymph nodes, but rarely through blood. This resulted in more metastasis to the pelvic organs than other areas as seen in colon and breast cancer [40-42]. Generally, the study estimated the incidence of the disease but not the prevalence; it's also included some resident patients from south Sudan country. Most of our studied patients received three cycles of treatment but no complications had been observed as a side effect of the treatment. Other studies recorded many complications, for instance ascites and edema especially after the fifth cycle [43]. Yet, no certain explanation had been identified.

The time duration between full treatment and relapse had been used to determine the response to the second line treatment [44]. The tumor relapse within three months was considered as platinum refractory, within six months as resistant and beyond that as sensitive [44]. According to this classification, our study categorized patients into two groups, platinum refractory and platinum resistant in equal per cent.

The tumor marker Cancer antigen (CA) 125 is considered as a gold standard tumor marker in ovarian cancer. Elevated levels of CA125 are used for monitoring the response to treatment [45], relapse, and progression of the disease as well [46]. In our study, we detected 25.8% of the patients returned their normal value of the CA125 (0-34 U/ml) after receiving the first line platinum treatment contrary to 79.4% who achieved the same value after receiving second line. Our results are in line with other studies that revealed better CA125 response with second line platinum treatment than initial chemotherapy. The alterations in CA 125 values depends on different factors such as agents interference with metabolism of the CA125 [47], tumor clone mix and agent affinity for tumor tissues expressing CA125 [47].

Gemcitabine is a pyrimidine antagonist agent that interrupts DNA synthesis by targeting specific cells in the S-phase [48], Gemcitabine is one of the most active drug agents in recurrent ovarian cancer and can be used both as combination therapy or single agent [49], Gemcitabine is mainly used as the second combine in ovarian cancer treatment as he shows more benefits and low associated side effect.

Conclusion

Age group above 55 years was the commonest affected age group. Al Jazeera state is the most geographical region treated by the second line of platinum resistance therapy. Serous adenocarcinoma is the most histological finding and pelvic organs are the most vulnerable organs for metastasis. Gemzar was found to be the most abundant chemotherapeutic agent been used and showed more than one-third curable rate. The value of CA125 reduced markedly after treatment. We thought that the results regarding the use of Gemzar may affect the practice of treatment of ovarian cancer by

second-line chemotherapy, but still, there is no solid confirmation about the most effective agent. Further studies are required to confirm the effectiveness of such therapy in treatment of platinum resistant ovarian cancer in Sudanese patients.

Declarations

Ethical Approval and Consent to Participate

Obtained from the federal ministry of health (FMOH), Khartoum, Sudan.

Consent for Publication

Not applicable

Availability of Data and Materials

All the data used in the study is available from the first and corresponding author on reasonable request

Competing of Interest

All authors declare that they have no conflict of interest.

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