

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

Mohammed Altyb Alshykh

Alzaiem Alazhari University

Mohammed Elmujtba Adam Essa (✉ Awadali818@yahoo.com)

MCRI <https://orcid.org/0000-0002-1050-2771>

Yousra Abdelmoniem Suleiman

Omdurman Islamic University Faculty of Medicine and Health Sciences

Sherihan Mohammed Elkundi Osman

Al Fashir University Faculty of Medicine

Mustafa Mohamed Ali Hussein

Al Fashir University Faculty of Medicine

Sadia Kamal Albadawi Mohamed

University of Gezira

Shiema Emad Abdelrahim

Omdurman Islamic University Faculty of Medicine and Health Sciences

Leena Habeeb Allah Osman

Omdurman Islamic University Faculty of Medicine and Health Sciences

Saja Hassan Mohamed

Omdurman Islamic University Faculty of Medicine and Health Sciences

Salma Ismaeel Rahama

Omdurman Islamic University Faculty of Medicine and Health Sciences

Saneyya Alsir Ali

Omdurman Islamic University Faculty of Medicine and Health Sciences

Sadiya Aminu Abdullahi

Omdurman Islamic University Faculty of Medicine and Health Sciences

Suha Abdallah Musa

Omdurman Islamic University Faculty of Medicine and Health Sciences

Abdelkareem A. Ahmed (✉ kareemo1511@gmail.com)

University of Nyala

Keywords: adenocarcinoma; Gemzar; ovarian cancer; second line chemotherapy

Posted Date: August 20th, 2019

DOI: <https://doi.org/10.21203/rs.2.13192/v1>

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Abstract

Background Ovarian carcinoma is the fifth leading cause of cancer death worldwide. The tumor mostly associated with variant factors such as advance age, early menstruation and gene association. We aimed to highlight the effectiveness of the second line chemotherapy in the management of ovarian cancer patients in Sudan. **Methods** The data were collected from the hospital patient's records for five years period of time, included 62 patients with ovarian cancer who is treated by the second line platinum resistant chemotherapy. **Result** The peak prevalence of the patients was found in Al-Gazeera state, and the least in Al-Gadarif state. Age group above 55 years was the most affected group. The vast majority of patients showed partially mass disappearing, completes and continue growing tumor respectively. All patients received variant cycles of chemotherapy as fellow 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 the 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 in all the patients and the least two types were observed are cell carcinoma and serous papillary. **Conclusion** Our findings suggested that, Al-Gazeera state citizens were more vulnerable to resist the first line chemotherapy than others. The Sudanese patients with ovarian cancer may have better response to Gemzar.

1. Background

Ovarian cancer is one of the most widely distributed malignancies worldwide and is considered the lethal gynaecological type and the fifth leading cause of cancer death (1–4), because of its high recurrence rate which is resist to chemotherapy (5). Nearly, 3 out of 4 of epithelial ovarian cancer (EOC) type present with late advanced stage (6). The lifetime risk of developing ovarian cancer in general population is 1.4 per cent and the mean age of presentation is 64 years, even though its incidence are varied by regions (7). Many factors play major role in the disease development and these includes advance age (8, 9), genetics associations (10–12), early menstruation (13), late menopause (14) and hormonal therapy (15). An ovarian tumors are mainly primary but secondaries from colon (16), stomach (17), small intestine (18), pancreas (6), breast (19) and even thyroid cancer (20) are also common. The world health organization (WHO) classified the ovarian cancer to many types based on their histological principles (21), the high grade serous ovarian carcinoma are considered the most common type (22). The current management of ovarian tumours at the early stage includes surgical removal (23, 24), followed by combination platinum/taxane chemotherapy (25, 26), while the others two thirds of patients which presented with advance late stage respond to the conventional therapy (27). 60% of them will have disease recurrence and up to 90% will die eventually (6). The survival rate in early stage patients approaches 90%, however most of ovarian tumors diagnosed in their advance stage (28). Ovarian tumors can originate from any site of the following potential three: fallopian tube (29), mesothelium lined peritoneal cavity (30) and ovary surfaces (31). The risk of metastasis of ovarian cancer depends on the stage and histological subtype of the tumor (32). Patients with recurrent EOC are characterized by an initial platinum therapy response (33). Women with ovarian cancer have a good response to standard platinum treatment (34),

although majority of patients with late stage will ultimately relapse (35), and resist the first line treatment (35, 36). Platinum resistant ovarian cancer is defined as disease recurrence within 6 months of completion of first-line platinum-based chemotherapy (37), and when cancer actually demonstrate growth during treatment or no frankly evidence of cancer regression after 4–6 cycles of therapy by platinum treatment (38). The platinum resistance has widely been demonstrated recently for ovarian cancer (5) and included many chemotherapy agents (39).

The decision of considering second-line chemotherapy in recurrent ovarian cancer patients is not yet fully clear, and this is related to the absence of standard chemotherapy to the recurrent ovarian cancer or the platinum-resistant (5). Until now oncologists are not capable to understand the genetic events for developing of ovarian tumors and it remains unknown. This is due to lack of an experimental model system for understanding and studying human ovarian tumor in contrast to several studies conducted using the animal models for ovarian carcinogenesis (40–43).

There are no information about the chemotherapy treatment of ovarian cancer in Sudan, Therefore we are aiming to determine the effectiveness of second line chemotherapy in 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.

2. Methods

This is a retrospective cross sectional hospital study carried out at The Radiation and Isotopes Centre Khartoum (RICK), Khartoum, Sudan, which was conducted between the periods of 2013–2017 for a number of 62 recurrent ovarian cancer patients. The data was 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 confirm cancer diagnosis by clinical oncologist including patient age, clinical presenting features, occupation, geographical, ethnic distributions, histopathological reports for ovarian cancer type, computer imaging (CT), CA 125value before and after treatment receiving, the interval time between full course given treatment and the cancer recurrence, and number of chemotherapy cycles. The patients received multiple agents of second line chemotherapy such as Gemzar in dosage of 1 gram as follow: each 7 days for 3 time then repeated every 3 weeks, carboplatin in a dosage of 30 mg/m² every 4 weeks for 3–6 cycles, Docetaxel 60–75mg/m² intravenous (IV) administration over 1 hour followed by carboplatin AUC 5–6 IV over 1 hour day 1 repeated every 3 weeks x 6 cycle. The ethical approval and formal consent was obtained from all the patients, the federal ministry of health (FMOH) and the ethical committee of the RICK for scientifically purpose.

2.3 Statistical analysis

Statistical software package SPSS version 17.0 has been used to analyze data of second line chemotherapy platinum resistance ovarian cancer such as percentages, frequency, valid percent and

cumulative percent. P value calculations for statistical significant testing, evaluations data were analyzed by one-way analysis of variance (ANOVA), the level of statistical significance was set as $P < 0.05$.

3. Results

Gemcitabine (Gemzar) found to be the most widely used chemotherapeutic agent by 72.6 % of all the studied patients, followed by Gemzar nevalbin 8.1 %, Gemzar cyclophosphamide 8.1 %, both Taxol & carboplatin 6.5 %, then Gemzar oxaliplatin 3.2 % and finally Docetaxel 1.6% (Table 1). All patients received various cycles of chemotherapy, in about 40.3 % of all the patients received 3 cycles of the chemotherapy. Patients who received 5 cycles and 1 cycle have the fewest percentage between all the patients only 6.4% of each. The other patients received different cycles of chemotherapy as follow: 21% of patients received 6 cycles, 17.7% have 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 by 43.5%. Abdominal ascites 24.2%, combined ascites and pelvic mass 16.1%, both pelvic and liver metastasis in same percentage 4.9%, and also liver metastasis with ascites with equal per cent 3.2%, pelvic and peritoneal metastasis 3.2%, isolated lung metastasis 3.2%, and lastly ascites with pelvic and lung metastasis together 1% (Table 3).

Regarding the chemotherapy agents effectiveness, patients who treated by Gemzar showed 42.2 % zero mass in the CT abdomen report, 46.7 % decreased masses size and 11.1% continuous increased mass size (Table 4). The most common histopathological type isolated from the patients were serous cyst adenocarcinoma in 90.3% of all the patients, followed by mucinous adenocarcinoma 3.2%, and the remaining types in equal percent 1.6, which are transitional cell adenocarcinoma, endometrial adenocarcinoma, serous papillary adenocarcinoma and clear cell carcinoma (Table 5).

For the tumor marker CA 125, there were 24.1 % of patients were sustained values before and after treatment. About 25.8 % have returned into the normal value and 1.6 % of the patients showed increases in the level 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 were reached the normal range of CA125 value (0–34 U/mL). Regarding the age groups, there were 37.1 % of the patients were above of 55 years old (Fig. 1). We also observed that both AlGazeera and Khartoum states had the highest and equal incidence among all the patients by 19 % (Fig. 2), followed Kordoufan states 16 %, white Nile state 15 %, Darfur states 8 %, Kassala state 8 %, Abuhammed city 7 %, AlGadarif 5 % and Republic of South Sudan 3 % (Fig. 2). In Half of the patients the tumor recurred after 1–2 months from full treatment course of the chemotherapy, followed by 32.3 % after 3–4 months and 17.7 % after 5–6 months (Fig. 3). After receiving the second line chemotherapy, 30.6 % of the patients showed complete mass disappearing with 54.8 % of regression in the mass size and 14.5% had failed to respond to treatment with increase in tumor size (Fig. 4).

4. Discussion

Many factors can contribute in the etiology of ovarian tumors, and these may include genetic mutation such as Breast Cancer (BRCA) mutation (44–47), postmenopausal stage (48), talcum powder (49) and hormonal change in advance age (50). Generally this type of cancer is considered to be one of the most devastating tumors, due to the lack of specific clinical symptoms related to it, until to be spread beyond level of the primary site and become difficult to treat (50). The current study demonstrated platinum resistance ovarian cancer patients for four years period of time. The study showed that an age group above 55 years was represented more than the one third of the patients. Our results are similar to earlier studies which reported that malignant ovarian cancer age incidence rate above 55 years (5, 51–53). Other reports revealed the age group above the 65 years, constitutes 30–40 % of all ovarian cancer patients (22, 54). This higher prevalence of age linked ovarian malignancy may related to menopausal period (14) and advance age (50).

Here we reported for the first time that both Al Gazeera and Khartoum states had the same incidence 19 %. But taken in account the population density between two states, the prevalence were higher in Al Gazeera state compared to Khartoum state 2:1 respectively (51). The second line platinum resistance chemotherapy included many types such as liposomal pegylated doxorubicin (55), topotecan (56), paclitaxel (57), oral etoposide (58) and gemcitabine (51). All of these chemotherapy agents have similar response treatment rate which is about 10 % (5). Our findings showed that the Gemzar had better response among other chemotherapeutic agents by 42.2% of the studied patients treated. In addition, Gemzar treatment showed complete response by 46.7% with partially shrinkage of tumor size and the remaining 11.1% of the patients resisted the treatment. Our findings mismatch with previous study that reported less effectivity of Gemzar to ovarian cancer patients, as only 18.5% of cases showed complete response, 29.6% with partially response and 51.9% with disease progression (22). This could be due to the antitumor activity and higher tolerability against toxicity (54, 59).

The serous cyst adenocarcinomas are the most isolated histological type, and had been identified in 90.3 % of our studied patients. Our results are in agreement with those reported from others studies which show the same isolated histological type (22, 50, 60–62). This may related to higher significant frequency number of abnormality genetics copy in adenocarcinoma type (63, 64), and absence of BRCA function (65). The pelvic mass was the most common metastatic site of ovarian cancer in our patients. And this is related to the unique nature of the ovarian tumor itself, where it tends to spread more easily by passive mechanism of the physiological movement to the peritoneum and omentum through the peritoneal fluids (30). Therefore, it disseminates by the pelvic and para-aortic lymph nodes but rarely through the vasculature (66). Unlike other types of cancer such as colon and breast cancer, and hence the pelvic organs are the most affected site of ovarian carcinoma (67, 68). Generally, the study estimated the incidence of the patients not the prevalence; it's also included some resident patients from south Sudan country. Most of our studied patients received three cycle of treatment but no complication had been observed as side effects despite of other studies who recorded many, for instance ascites and edema especially after the fifth cycle (69). Yet, no certain explanation had been identified.

The interval time duration between full treatment and relapse had been used to determine the condition response of the second line treatment (70). The tumor relapse within three months is considered platinum refractory, six months resistant and beyond that as sensitive (70). According to this classification, our study categorized patients into two groups, platinum refractory and platinum resistant in equal percent.

The tumor marker Cancer antigen (CA) 125 is considered a gold standard tumor marker in ovarian cancer (71). Elevated levels of CA125 are used for monitoring treatment response (72), relapse (73), and progression of the disease (74). 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 in contrary to 79.4% who achieved the same value after receiving second line. Our results are in line with other study that revealed better CA125 response in second line platinum treatment than initial chemotherapy (75). The alterations in CA 125 values depend on different factors, such as agents interference with metabolism of the CA125 (76), tumor clone mix (76) and agent affinity for tumor tissues expression of CA125 (76).

The limitation of our study is no BRCA testing was available to the patients.

5. Conclusion

Age group above 55 years was the commonest affected age group. Al Gazeera state is the most geographical region treated by the second line platinum resistance. Serous adenocarcinoma is the most histological finding and pelvic organs are the most vulnerable organs to metastasise. Gemzar was found to be the most abundant chemotherapy agent been used and showed more than one third curable rate. The value of CA125 has reduced markedly after treatment. These findings could enhance establishing a new guideline for treatment of ovarian cancer by second line chemotherapy.

6. Declarations

6.1. Ethical approval and consent to participate

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

6.2. Consent for publication

Not applicable

6.3. Availability of data and materials

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

6.4. Competing of interest

All authors declare that they have no any conflict of interest.

6.5. Funding

No fund have been received

6.6. Author contributions

The scientific writing of the manuscript along with the data analysis were handle it by Dr. Mohammed Elmujtba Adam Essa, Dr. Mohammed Altyb Alshykh, Dr.Sherihan Mohammed Elkundi Osmanand Dr, Mustafa Mohamed Ali Hussein, Dr. Sadia Kamal Albadawi Mohamed, The data were collected from the hospital records by Shiemaa Emad Abdelrahim, Leena Habeeb Allah Osman, Saja Hassan Mohamed, Salma Ismaeel Rahama, Saneyya Alsir Ali,Sadiya Aminu Abdullahi and Suha Abdallah Musa. Dr.Yousra Abdelmoniem Suleimanis the clinical oncologist who supervised the treatment of the patients. The study was supervised by Prof. Abdelkareem A. Ahmed.

6.7. Acknowledgments

The authors are highly grateful to RICK hospital administration for their support to conduct this research

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8. Tables

Table: 1 illustrate the second line chemotherapy agents.

Second line chemotherapy agents	Frequency	Per cent
Gemzar	45	72.6 %
Taxol & carboplatin	4	6.5 %
Docetaxel	1	1.6 %
Gemzar nevalbin	5	8.1 %
Gemzar oxaliplatin	2	3.2 %
Gemzar cyclophosphamide	5	8.1 %
Total	62	100 %

Table: 2 show the frequencies of each cycle of the second line platinum resistance chemotherapy received by the ovarian cancer patients.

Chemotherapy cycles	Frequency	%
1	2	3.2 %
2	11	17.7 %
3	25	40.3 %
4	9	14.5 %
5	2	3.2 %
6	13	21%
Total	62	100 %

Table: 3 show The CT abdomen reports of the patients.

Computer tomography scan findings	Per cent	Frequency
Pelvic mass	43.5 %	27
Lung metastasis	3.2 %	2
Ascites	24.2 %	15
Pelvic mass & liver metastasis	4.9 %	3
Pelvic mass & peritoneal metastasis	3.2 %	2
Pelvic mass & Ascites	16.1 %	10
Liver metastasis & Ascites	3.2 %	2
Pelvic mass, lung metastasis & Ascites	1.6 %	1
Total	100 %	62

Table: 4 demonstrate the metastasis site, percent and frequencies of the patients before receiving the second line chemotherapy.

Chemotherapy agent	Complete responded	Partial responded	Failed responded	to Total
Gemzar	19	21	5	45
	42.2 %	46.7 %	11.1 %	100 %
Taxol & carboplatin	0	4	0	4
	0.00 %	100 %	0.00 %	100 %
Docetaxol	0	1	0	1
	0.00 %	100 %	0.00 %	100 %
Gemzar & nevalbin	0	3	2	5
	0.00 %	60 %	40 %	100 %
Gemazr & oxaliplatin	0	1	1	2
	0.00 %	50 %	50 %	100 %
Gemazr & cyclophosphamide	0	4	1	5
	0.00 %	80 %	20 %	100 %
	19	34	9	62
	30.6 %	54.8 %	14.5 %	100 %

Table: 5 show the histopathological types of ovarian cancer.

Histopathological types	Frequency	%
Serous cyst adenocarcinoma	56	90.3 %
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 %
Total	62	100 %

Figures

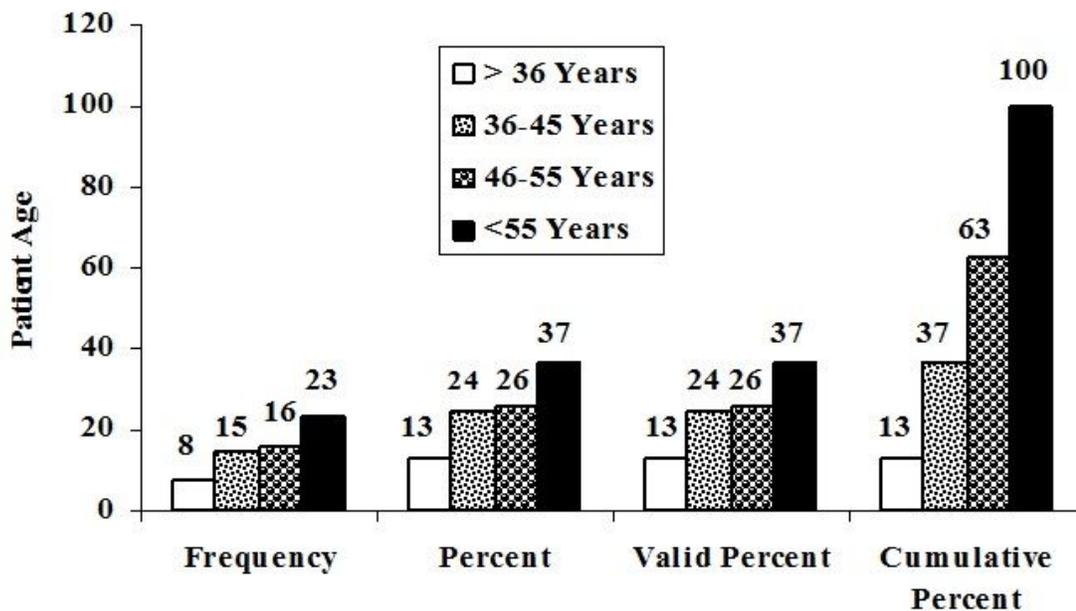


Figure 1

Fig: 1 demonstrates the age distribution of the patients.

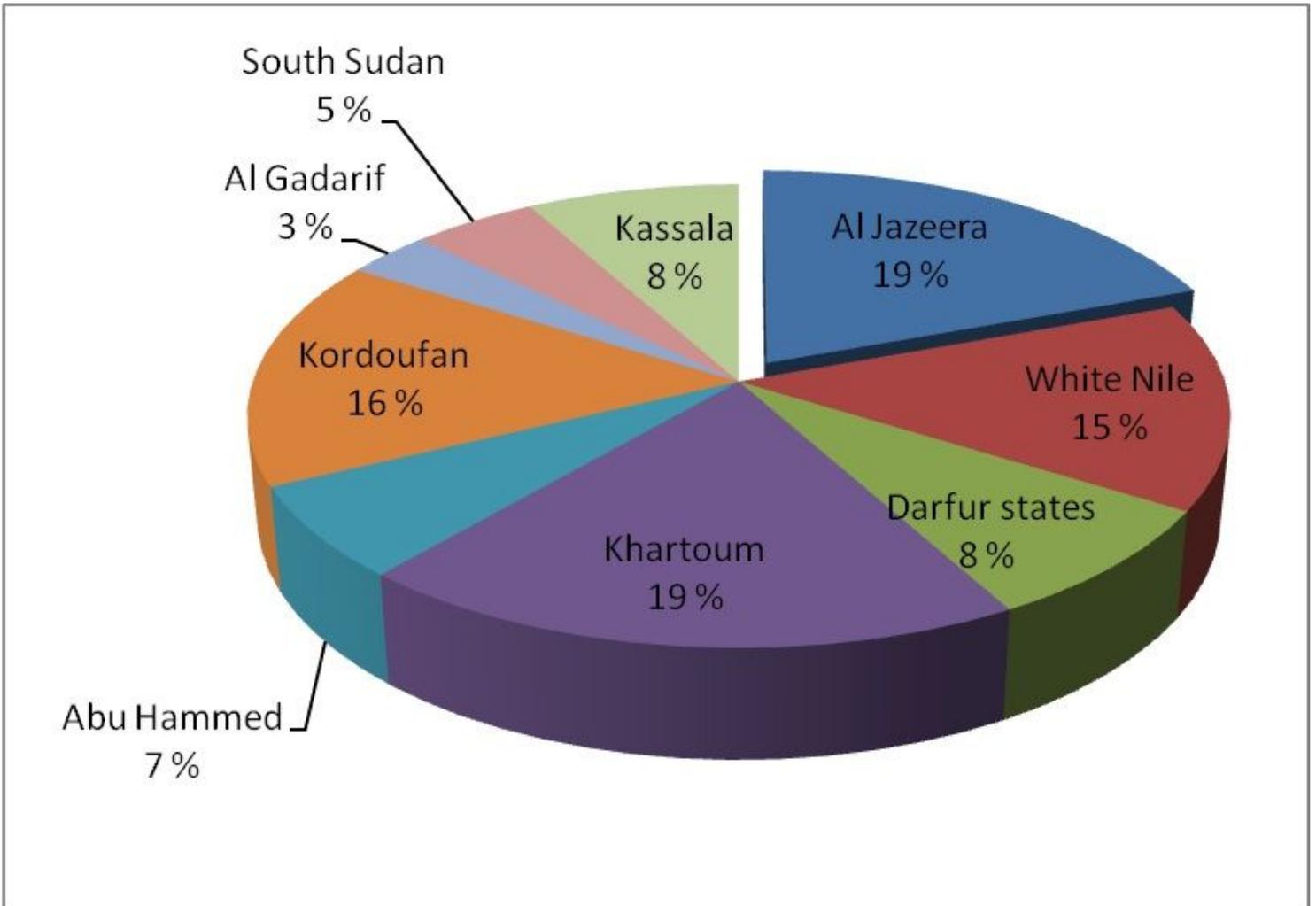


Figure 2

Fig: 2 the geographical distribution of the patients treated with second line chemotherapy platinum resistant ovarian cancer in Sudan.

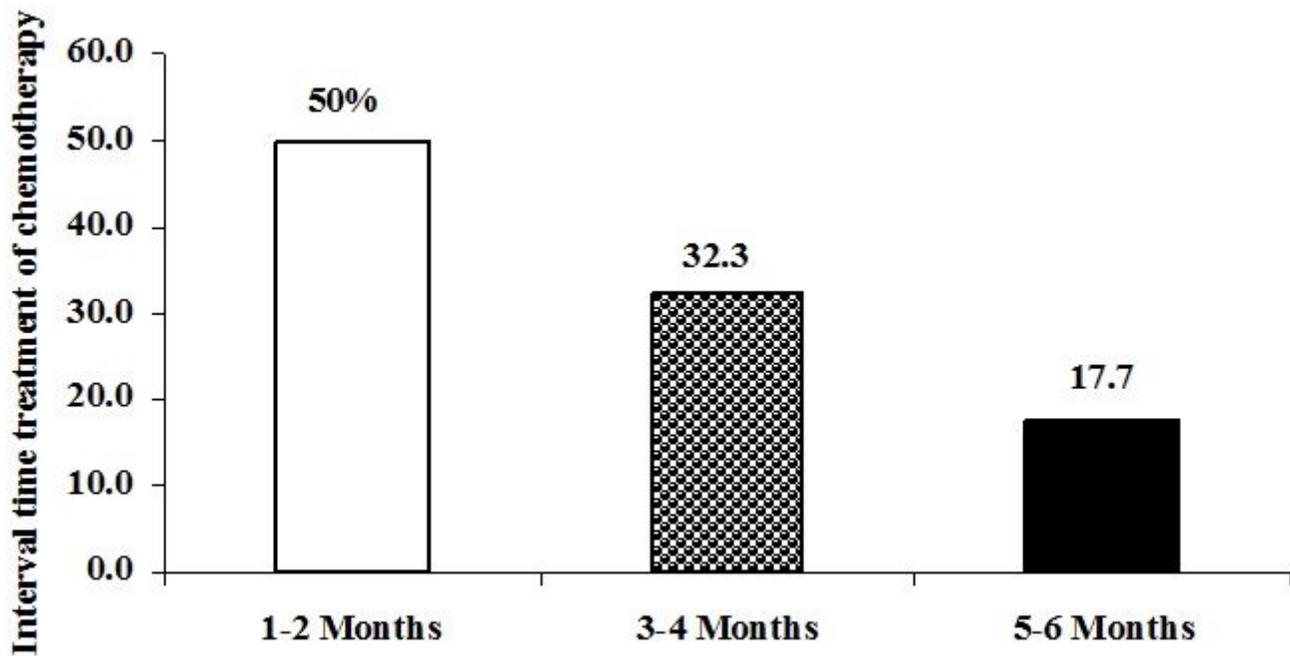


Figure 3

Fig: 3 show the time interval in all the between the complete course of the second line platinum resistance chemotherapy and the disease recurrence.

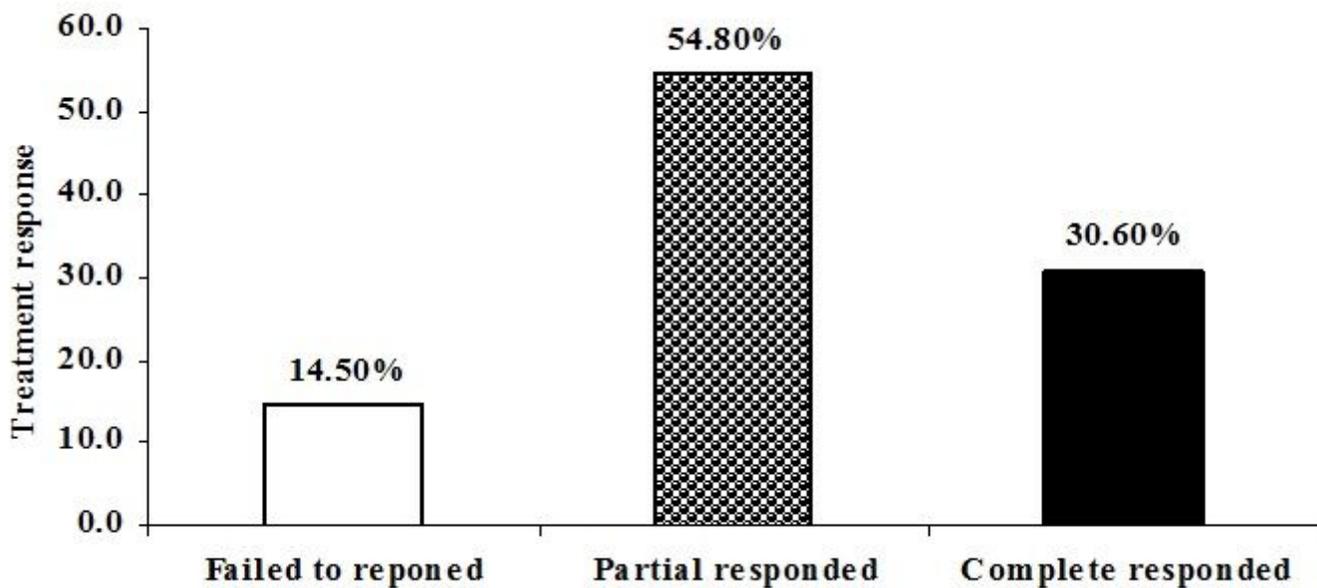


Figure 4

Fig: 4 show the second line platinum resistance chemotherapy to the ovarian cancer patients.