Role Of Cisplatin And Cyclophosphamide Chemotherapy In Bulky Residual Disease After Primary Cytoreductive Surgery Of Epithelial Ovarian Cancers

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From May 1993 to June 1997, 58 patients with bulky residual disease after primary cytoreductive surgery of epithelial ovarian cancer were treated with cisplatin and cyclophosphamide combination chemotherapy. Overall responses were seen in 30 patients (51.72 %) with complete responses in 9 patients (15.51 %) and partial responses in 21 patients (36.11 %) at 4 months. 28 patients (48.27 %) were non-responders. Response in relation to the size of residual disease revealed that 24 out of 36 patients (66.66 %) did not show a complete response to chemotherapy. It is concluded that bulky residual disease of greater than 4 cm responds poorly to cisplatin and cyclophosphamide combination chemotherapy.

Key Words: Cytoreduction surgery, chemotherapy, and ovarian tumour

Platinum containing combinations became a standard treatment for advanced epithelial ovarian cancer in 1980's as these provided consistently better results than non - platinum containing regimens[1-3]. The largest trial was conducted by Gynaecologic Oncology Group in which patients who received cyclophosphamide plus adriamycin were compared to patients who received cyclophosphamide, adriamycin and cisplatin (CAP) combination chemotherapy. The CAP regimen showed a better response rate, longer response duration, longer progression - free duration and an improved overall survival[3]. In early 1990's, a metaanalysis of 45 such trials confirmed the survival benefit for cisplatin based treatment[4]. With the development of less toxic analogue, carboplatin, several trials compared single agent carboplatin to cisplatin in previously untreated patients with advanced disease and found similar survival with both drugs[5]. Similarly, cisplatin containing combinations were compared with carboplatin containing combinations and no survival difference was found[6-8].

Subsequently, combination of cisplatin and cyclophosphamide (CP) was compared against adriamycin containing combinations of PAC and CHAP-[5] and no significant difference was reported with regards to overall survival, progression- free survival and response rates [9-10]. Thereafter, the CP regimen became the standard of treatment for advanced ovarian cancer. Although, the two metaanalyses and a large Italian trial subsequently demonstrated a higher response rate and a survival advantage for patients treated with adriamycin containing regimens[11-13], the CP regimen continued to be the first line chemotherapy in most parts of the world with the exceptions of some European countries[14].

Later paclitaxel, a new class of cytotoxic drugs was introduced and the combination of paclitaxel plus cisplatin was compared against CP combination in patients with sub-optimally resected Stage III & IV patients by Gynaecologic Oncology Group[15]. The paclitaxel plus cisplatin combination proved superior to CP regimen in terms of response rates, progression-free survival and overall survival.

In mid-1990's, the combination of paclitaxel and cisplatin became established as a standard of care for the treatment of advanced epithelial ovarian cancer[14]. The cost of this combination is prohibitive and the CP regimen, a much cheaper combination, continues to be the first line chemotherapy in the majority of the patients with advanced disease in Pakistan. This study analyses the response rates and pattern of failures in advanced stage patients treated with CP combination chemotherapy.

Patients And Methods

From May 1993 to June 1997, 58 patients with bulky residual disease after primary cytoreductive surgery for epithelial ovarian cancers were treated with cisplatin and cyclophosphamide combination chemotherapy at Jinnah Hospital Lahore. The medical records of these patients were evaluated to determine the patient's age, surgical stage, histopathology, grade, size of post-surgical residual disease and response to chemotherapy. Patients were evaluated before chemotherapy with complete blood count, liver function tests, urea, creatinine, creatinine clearance and urine examination, serum albumen levels, serum electrolytes, chest X-ray and ECG. Post-surgical residual disease was measured by abdominopelvic ultrasonography. Performance status was recorded on KPS scale. Chemotherapy protocol and doses were evaluated from chemotherapy flow charts. Cisplatin 75mg / m2 / IV D1 and cyclophosphamide 750mg / m2 / IV D 1 were given to 32 patients with cycles repeated every 3 weeks.

Cisplatin 20mg / m2 / IV D1-5 and cyclophosphamide 600mg / m2 / IV D4 was given to 26 patients with cycles repeated every 3 weeks. Responses were evaluated by serial ultrasound examination of bidimensionally measurable disease (BDMD) in all patients at 2,4 and 6 months. Fifteen patients with serous adenocarcinoma were also evaluated by CA-125. Response evaluation was done according to the following criteria:

Complete response was defined as the complete disappearance of all objective evidence of disease for at least 4 weeks. Partial response was defined as greater than or equal to 50% decrease in the sum of the products of the two largest perpendicular diameters of all measurable disease lasting for at least 4 weeks and without the appearance of new lesions. No response was defined when a 50% decrease in total tumor size could not be established nor a 25 % increase in the size of one or more measurable lesions could be demonstrated. Patient characteristics are given in Table 1.

Table 1: Patient Characteristics

No. Evaluable		58
Age in Years		
Median		45
Range		28-74
Performance Status (KPS)		
50-70		36
70-80		16
➢ 80		06
FIGO Staging		
II		08
III		42
IV		08
Histopathology		
Malignant	Serous	38
Tumors		
Malignant	Mucinous	20
Tumors		
Grade		
II		12
III		32
Unknown		14

Results

Overall responses were seen in 30 patients (51.72 %) with complete responses in 9 patients (15.51 %) and partial responses in 21 patients (36.20 %) at 4 months. Twenty-eight patients (48.27 %) were non-responders. Response in relation to the size of the largest residual disease is shown in Table II. 4 out of 22 patients (18.17 %) with a size of residual disease of >2-4 cm and 16 out of 28 patients (57.19 %) with a size of residual disease of >4-6 cm were non-responders. All 8 patients with residual disease of >6 cm were non-responders. Grouping together all the patients with residual disease of >4cm it is apparent that 24 out of 36 patients (66.66 %) did not show a response.

Table II: Response in relation to size of residual disease (n=58)

Size in cms	CR No. (%)	PR No. (%)	NR No. (%)
>2-4 (22)	7 (31.81%)	11 (50.0%)	4 (18.18%)
>4-6 (28)	2(7.14%)	10 (39.28%)	16 (57.14%)
>6 (8)			8 (100%)

Discussion

Present analysis has shown that 52.72% patients with bulky residual disease after primary cytoreductive surgery achieved an overall response and 15.51 % achieved a complete response to cisplatin based chemotherapy. Whereas, in a majority of other studies similar response rates varying from 40-60 % have been reported[9,15]. However, the complete response of 15.51 % seen in these patients is significantly lower than the generally reported complete response rates of 30-40 % [9,11]. A pathological response rate of 20-23 % has been documented in many sereis[15,16]. No such pathological complete response was documented in our patients.

Considering the size of residual disease it is evident that 66.66% of patients with largest diameter of disease >4cm did not respond to chemotherapy. Majority of studies do not specify the exact extent of residual disease greater than 2cm. The response data according to the different sizes of residual disease is therefore not available. However, it seems logical that with increasing size of residual disease the chances of a complete response shall decrease.

It was the initial findings of Griffith[17], that survival was directly affected by the initial degree of cytoreduction in women with advanced ovarian cancer. A large number of subsequent studies and metaanalyses confirms that patients with no residual disease and residual disease less than or equal to 2cm after surgery for stage III and IV disease have better survival than the patients with tumor mass greater than 2cm [18-20]. Similarly women with no gross residual disease or residual disease with less than 2cm diameter treated with cisplatin based chemotherapy had better response rates and better survival[21]. It seems that for the best possible outcome, optimal cytoreductive surgery and treatment with a platinum based combination chemotherapy is required. Optimal primary cytoreduction today means that no tumor mass >1cm is left behind[14]. Unfortunately, the majority of our patients do not achieve an optimal primary cytoreduction. Apparently, it seems to be related to the

technical abilities and facilities, but it might be related to the biology of the tumor. Possibly, more aggressive tumors present with such a large disease that optimal cytoreduction is not possible. This idea can be further strengthened from the findings of Hoskins et al who suggested that, contrary to the earlier reports, women undergoing optimal cytoreductive surgery do not have survival equivalent to the women who have a small volume disease at presentation. In his series women who had optimal cytoreduction and small residual diseases of 1 cm or less were compared to 200 women with initial disease of 1 cm or less and were found to have poor survival outcome. Indeed, the best survival results were seen in women who had tumor initially smaller than 1 cm[22]. This definitely reflects on the importance of biologic behavior of ovarian cancer, and indicates that the sub-optimally cytoreduced might have more aggressive tumors. But the size of residual disease after sub-optimal cytoreduction remains an important factor as is evident in this analysis the larger tumor residues failed to respond.

Emergence of drug resistance seems to be another factor responsible for chemotherapy failure. Resistance to platinum compounds is multifactorial and a single method to reverse the resistance is unlikely to emerge. Improvement in the treatment of advanced ovarian cancer may come with the use of neoadjuvant chemotherapy, improved cytoreductive technique, use of new drugs or with the reversal of drug resistance.

It is concluded that bulky residual disease of greater than 4 cm poorly responds to cisplatin and cyclophosphamide combination chemotherapy.

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