Original Research Article

Carboplatin - based chemotherapy in advanced ovarian cancer

E. A. Ashok Kumar[1*], P. Jijiya Bai[2]

[1]Professor, Department of Medicine, MNR Medical College and Hospital, Fasawadi, Sanga Reddy, Medak, Telangana, India
[2]Professor, Department of Pathology, MNR Medical College and Hospital, Fasawadi, Sanga Reddy, Medak, Telangana, India
[*]Corresponding author email: **ashokedla@gmail.com**

International Archives of Integrated Medicine, Vol. 3, Issue 7, July, 2016.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 02-06-2016 **Accepted on:** 15-06-2016
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: E. A. Ashok Kumar, P. Jijiya Bai. Carboplatin - based chemotherapy in advanced ovarian cancer. IAIM, 2016; 3(7): 5-10.

Abstract

Eight patients of advanced ovarian cancer were treated with monthly cycles of Ifosfamide, Adriamycin and Carboplatin. Debulking surgery was done in 7 cases. None of the patients had complete response. All eight patients had partial response. The follow-up was for 36 months. The present protocol appears to have an influence on initial control of disease but relapse continue to occur following the treatment. Cytoreductive surgery before or after three cycles of chemotherapy may have favourable influence on disease free survival (DFS). Second, third, fourth look surgeries have good results in many centers, which is not routinely practised at this center, might be the main reason for the poor outcome. Prolonged follow up along with second, third, fourth look surgeries will be necessary to determine the overall influence on long term survival.

Key words

Carboplatin, Ovarian cancer, Second look surgery.

Introduction

Remarkable changes in the management of ovarian cancer took place in the last twenty years. Alkylating agents have been the most commonly used drug as single agents. A revolutionary concept evolved, demonstrating the superiority of multiple drug combination over single drug chemotherapy in advanced ovarian cancer. The achievement of high overall response rates in advanced ovarian cancer using cisplatin-based combination regimens has been confirmed by several investigators [1]. Cisplatin was replaced by Carboplatin, because it was better tolerated with an improved quality of life [2, 3].

The development of active chemotherapy for ovarian cancer during early 70's was the instigating force that established the role of second look surgery, which was first advocated over 50 years ago, to monitor the progress of the patients on chemotherapy for ovarian cancer [4].

Second-Look Laparotomy for Ovarian Carcinoma [4]

Second - look laparotomy means a repeat laparotomy in a patient without clinical evidence of disease following an interval of chemotherapy.

″Patients with persistent tumor, identified by the surgeon and confirmed by the pathologist, are regarded as having a **macroscopically positive second look**. When the surgeon cannot identify any suspicious areas, but either cytologic washings or multiple staging biopsies disclose persistent tumor, it is called a **microscopically positive second look.**. When there is neither cytologic nor histologic evidence of persistent tumour, the patient is considered to have a **negative second look**.When the exploration is incomplete because of extensive adhesions, the second-look should be regarded as **inadequate**″.

In the patient with no evidence of persistent tumor, the avoidance of future chemotherapy may prevent acute leukemia(melphalan and other agents), neurotoxicity (cisplatin, hexamethylmelamine, and vincristine), nephrotoxicity (cisplatin), cardiotoxicity (doxorubicin), and other undesirable side effects. Although very few patients will benefit from extensive tumor reduction at second-look, patients with minimal disease may benefit from additional therapy based on the second-look findings.

The optimal duration of chemotherapy is variable ,and for a specific patients is unknown. Historically, the duration of treatment programs were developed on a trial and error basis [5]. The standard time interval to second-look laparotomy became 12 courses of chemotherapy, usually about 12-14 months from time of intial exploration.

The technique consists of

- Random biopsies are taken from the cul-de-sac (two)
- bladder peritoneum (two)
- both pelvic side-walls (four)
- both paracolic recesses (four)
- residual omentum (two or three)
- diaphragm (two)
- paraaaortic lymph nodes adjacent to the renal vessels.

The 5-year survival for advanced ovarian cancer is estimated at 30%. Does the absence of tumor at second-look (negative second-look) imply the patient is cured? No,there is a recurrence rate of 25-30% over the following 5 years. Is there a high-risk profile for patients developing recurrence? Yes, patients with either grade 3 tumors or grossly visible disease at completion of their initial surgery are at significantly greater risk for recurrence.

Does the presence of tumor at second-look carry with it a poor prognosis? Not necessarily. In contrast, the 5-year survival rates of microscopically positive grade 3 tumor was 36%. The most difficult problem of all lies with those patients who have macroscopic positive second-look findings. After recieving a cisplatin-containing chemotherapy combination, what treatment will be effective for these patients?

At present, the second-look laparotomy is the most reliable method of evaluating the disease status of a patient treated with chemotherapy for ovarian carcinoma [4].

Materials and methods

Women of 18 years of age or older with histologically proven epithelial ovarian carcinoma were recruited for the study, from February, 1990 To February, 1992. Total No. of patients were 8. The study was conducted at M N J Institute of Oncology, Hyderabad, and had ethics committee approval from the same institute.

Staging of carcinoma ovary was done, according to FIGO staging.

Inclusion criteria

- International Federation of Gynecologic Oncology (FIGO) stage II–IV,
- Eastern Cooperative Oncology Group performance status 0–2,
- No prior chemotherapy or radiotherapy, adequate hematologic, hepatic and renal function defined as absolute neutrophil count >1.5x10^9 cells per litre, platelet count at least 100x10^9 cells per litre, serum creatinine and total bilirubin not more than 1.25 times the upper normal limit.

Exclusion criteria

- Mixed mesodermal tumors, borderline tumors,
- Concurrent malignancies within the previous 5 years
- Pregnancy and lactation,
- Peripheral neuropathy grade 2 or higher,
- Congestive heart failure and cardiac arrhythmias.

Protocol consisted of HEP X 6 Cycles

H – HOLOXAN – 2000 TO 2400 mg/m^2 BSA – Day 1

E – EPIRUBCIN – 40 mg/m^2 – Day 1

P – CARBOPLATIN – 20 mg/m^2 BSA – Day 1 to Day 5

Cycle repeated every month for 6 months

Follow-up for each patient consisted of a physical examination every month after chemotherapy, and monitoring of chest X-ray, ultra sound of abdomen and pelvis, renal parameters and hemotological profile were done to see the response to treatment. Follow up was done up to 36 months.

Definition of response

Partial response

It is defined as a decrease in the size of a palpable tumour by 50% or more, for atleast three months, with subjective as well as objective improvement of the patient.

Complete response

It is defined as the total disappearance of all previously measurable tumor including ultrasound.

Therapeutic failures

Patients who had signs of progressive disease or no change in signs and symptoms during the time of treatment were considered therapeutic failures. Second look laparotomy was not done.

Results

Ovarian cancer was more common in 3rd to 5th decade (**Table - 1**). The most common symptom was abdominal swelling (**Table - 2**). Parity was not relevant for this cancer (**Table - 3**). Menstrual history was not relevant in this cancer (**Table - 4**). Only two patients had cancers in their parents (**Table - 5**). Obstetric history, masses per abdomen, Histopathology of the tumour, Ascitic fluid analysis, and Staging of the disease, Surgical procedures done, and there was only partial response in all the cases (**Table - 6**). There were multiple bilateral masses in 2 patients and bilateral single ovarian masses in 6 patients (**Table - 7**). Histopathologically cystadenocarcinomas were present in 4 cases (**Table - 8**). There was no ascitis in 4 cases, one patient had evidence of hemorragic ascitis with malignant cells, and 3 had only hemorrhagic ascitis (**Table - 9**). There were 4 patients in stage – Ib, 1 in stage- III and 3 were in stage – IV (**Table - 10**). Surgery was done in 7 cases and not done in 1 case. Total abdominal hysterectomy with bilateral salpingo oopherectomy in 6 cases, and in one case right ovariectomy was done (**Table - 11**). There was partial response in all the cases which were followed up to 36 months (**Table – 12**).

There were no Allergic reactions. There were no cases of cardiovascular toxicity, vascular toxicity, hemotological and renal toxicity.

Second look surgery – Not done in any case

Table – 1: Age distribution.

Age (Years)	Number of patients
21 – 30	2
31 – 40	2
41 – 50	2
51 – 60	1
61 – 70	1

Table – 2: Symptoms.

Symptom	No. of patients
abdominal discomfort	3
abdominal swelling	4
difficulty in passing urine	1
dyspnoea	2
bleeding per vaginum	1

Table – 3: Obstetric history.

No. of pregnancies	No. of patients
7	1
4	4
1	3

Table – 4: Menstrual history.

Menstrual history	Number of patients
Regular	5
Irregular	3
Menorrhagia	1

Table – 5: Family history of cancers.

No. of patients	Family history of cancers	Pathology of cancers
1	Mother	Carcinoma of ovary
1	Father	Carcinoma of stomach
6	None	None

Discussion

Ovarian cancer is usually diagnosed in the later stages due to the non-specifity of symptoms and non-availability of reliable screening methods at an early stage, resulting in an increasing tumour burden at presentation; the tumour at this stage is not curable by surgery or radiotherapy [6]. The poor prognosis of the disease in an advanced stage has prompted various workers to look for effective chemotherapy regimens. Although a number of chemotherapeutic agents are effective in ovarian cancer [7], cisplatin based combination regimens have been preferred recently because they yield high response rates in advanced disease [8]. The drug is also effective in resistant tumors [9] and can thus also be used in patients having failed on other drugs.

Table – 6: Obstetric history.

Number of children	Number of patients
More than 4	5
Less than 4	3

Table – 7: Masses per abdomen.

Number of masses	No. of patients
Multiple bilateral masses	2
Bilateral single ovarian masses	6

Table – 8: Histopathology.

Tumor histopathology	No. of patients
Papillary cystadenocarcinoma	2
Pseudomucinous cystadenocarcinoma	2
Teratocarcinoma	1
Anaplastic ovarian dysgerminoma	1
Granulosa tumor	1
Endodermal sinus tumor	1

Table – 9: Ascitic fluid analysis.

Ascitic fluid analysis	No. of patients
Hemorrhagic	3
Hemorrhagic with malignant cells	1
No ascitis	4

Table – 10: Staging of the disease.

Staging	Number of patients
I B	4
III	1
IV	3

Table – 11: Surgical procedures done.

Surgical procedure	No. of patients
Total abdominal hysterectomy with bilatral salpingooopherectomy	6
Right ovariectomy	1
No surgery	1

Table – 12: Response to chemotherapy.

Response	Number of patients
Partial response	8
Complete response	0

The tumor burden as determined by stage at presentation and residual disease after surgery is an important prognostic factor. Most of our patients underwent surgery before being referred to us; the exact extent of residual disease in them was not known. Since all our patients were having advanced stage disease, the tumour burden was considerable.

Although the extent of residual disease after surgery in our patients was not known, the impact of debulking surgery was obvious. The relapse rate was higher in those who did not undergo surgery [10]. This emphasises the fact that cytoreduction by surgery followed by chemotherapy prolongs the disease free survival. Approximately fifty percent of patients showing clinically no evidence of disease are positive for disease on second look surgery [11]. Relapse is known to occur after surgically documented complete remission [5].

The duration of chemotherapy in the management of advanced ovarian cancer is controversial. It is apparent that there is a group of patients who will respond to treatment, and continuation of chemotherapy beyond six cycles is not justified as this would cause unnecessary toxicity without any therapeutic gain. Regimens containing high dose of cisplatin, carboplatin, etoposide and ifosfamide have yielded promising results in advanced and refractory ovarian cancer [3, 9, 12], their use in primary management of advanced ovarian cancer may increase the cure rate and should be tried prospectively.

References

1. John D. Hainsworth, William W. Grosh, Lonnie S. Burnett, Howard W. Jones Iii, Steven N. Wolff, F. Anthony Greco. Advanced Ovarian Cancer: Long-Term Results of Treatment with Intensive Cisplatin-Based Chemotherapy of Brief Duration. Ann Intern Med., 1988; 108(2): 165-170.
2. du Bois A, Luck HJ, Meier W, Adams HP, Mobus V, Costa S, Bauknecht T, Richter B, Warm M, Schroder W, Olbricht S, Nitz U, Jackisch C, Emons G, Wagner U, Kuhn W, Pfisterer J. Arbeitsgemeinschaft Gynakologische Onkologie Ovarian Cancer Study Group (2003) A randomized clinical trial of cisplatin/paclitaxel vs carboplatin/ paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst., 2003; 95(17): 1320– 1329.
3. Ozols RF, Bundy BN, Greer BE, Fowler JM, Clarke-Pearson D, Burger RA, Mannel RS, DeGeest K, Hartenbach EM, Baergen R. Gynecologic Oncology Group (2003) Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol., 2003; 21(17): 3194–3200.
4. Larry J. Copeland. Second - look laparotomy for ovarian carcinoma. Clinical obstetrics and gynecology, 1985; 28: 816-822.

5. Greco FA, Julian CG, Richardson RL, et al. Advanced ovarian cancer: brief intensive combination chemotherapy and second look operation. Obstet Gynecol., 1981; 58: 199-205.
6. Declose L, Quinlan E.J. Malignant tumours of the ovary managed with postoperative megavoltage irradiation. Radiology, 1969; 93: 659 – 663.
7. DePalo G.M., Delena M, Di Re F, Luciani L, Valagussa P, Bonodonna G. Melphalan versus adriamycin in the treatment of advanced carcinoma of the ovary. Surg Gynecol Obstet., 1975; 141: 899-902.
8. B. S. Charak, S. Agarwal, R. Gopal, S. H. Advani, et al. Cisplatin- based chemotherapy in advanced ovarian cancer. Initial experience in an Indian set –up, 1989; 26: 85-91.
9. Barker G.W., Wiltshaw E. Use of high dose cis-dichlorodiammine platinum (ii) following failure on previous chemotherapy for advanced carcinoma of the ovary. Br. J. Obstet Gynecol., 1981; 88: 1192-1199.
10. Ehrlic C.E., Einhorn L, Williams S.D., Morgan J. Chemotherapy for stage III-IV epithelialovarian cancer with cis-dichlorodimmine platinum (II), adriamycin and cyclophospamide: a preliminary report. Cancer Treat Rep., 1979; 63: 281-288.
11. Free K.F., Webb M.J. Second look laparotomy – clinical correlations. Gyencol Oncol., 1987; 26: 290-297.
12. De Lena M, Lorusso V, Romito S. Cisplatin plus etoposide as second line treatment in advanced ovarian carcinoma. Cancer Treat Rep., 1986; 70: 893-895.