Case Report

Intraperitoneal Chemotherapy Following Refractory Intravenous Route in Advanced Ovarian Cancer

Shafiee MN[1], Omar MH[1], Suraya A[2], Hatta M[1]

[1]Gynae-oncology Unit, Department of Obstetrics and Gynaecology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000, Kuala Lumpur, Malaysia.

[2]Department of Radiology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000, Kuala Lumpur, Malaysia.

Abstract

Platinum based adjuvant chemotherapy is generally recommended for ovarian cancer to improve the survival rate. Intravenous route is commonly used, easily administered and less associated complications. However, intraperitoneal route is gaining its popularity as a single procedure or adjunctive to the intravenous route. Numerous questions on its eligibility and safety are still perplexed. A case review on a patient with non optimal debulking surgery of advanced ovarian cancer was studied. Intravenous platinum based chemotherapy combined with paclitaxel failed to bring her to clinical remission. Second line chemotherapy, gemcitabin rendered her to poor response with unresolved debilitating ascites needing recurrent drainage. Surprisingly, a trial of intraperitoneal chemotherapy with cisplatin revealed a great response with a complete clinical remission.

Keywords: Adjuvant, chemotherapy, cisplatin, intraperitoneal, ovarian cancer

Correspondence:

Dr. Mohamad Nasir Shafiee, Department of Obstetrics and Gynaecology, Universiti Kebangsaan Malaysia Medical Centre, Jalan Yaacob Latif, Bandar Tun Razak, Cheras, 56000, Kuala Lumpur, Malaysia. Tel: +603-91455949 Fax: +60391738946 Email: nasirshafiee@hotmail.com or mns@ppukm.ukm.my

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Introduction

Advanced stage ovarian cancer theoretically has a poor 5-year survival rate of approximately 30%–50% for stage III disease (1). Generally accepted management of ovarian malignancy includes staging laparotomy and primary optimal debulking followed by adjuvant intravenous chemotherapy (2). Neoadjuvant chemotherapy followed by interval debulking is reserved for the inoperable cases where subsequent surgery is aimed at complete clearance of the tumour mass in chemosensitive patients.

Intravenous chemotherapy which consist of platinum based agents (carboplatin and cisplatin) and taxane are extensively studied in order to obtain optimal response and prolonged remission resulting to improve survival rate. Yet, in many areas, it still remains implausible to achieve the goals and the management strategies mainly depending on the individual assessment. Although intraperitoneal (IP) chemotherapy is considered as an acceptable option for ovarian cancer with small residual tumour following a debulking surgery, and has shown an improvement in median survival rate by approximately 16 months, (2,3) but it is not widely practiced.

By biological rationale, ovarian cancer largely confined to the peritoneal cavity, which IP is an ideal treatment for residual disease. The efficacy of the IP chemotherapy has been widely tested in phase 1/11 clinical trials with established result in its pharmacokinetic actions and safety profiles. Therefore, this approach is deemed a vital alternative to consider

in such patients after first or second line treatment. In a small volume disease less than 1 cm, 30-40% had responded to IP cisplatin (2,3). More recently, paclitaxel was found to have distinct pharmacological advantages when administered intraperitoneally (4,5,6). The disease-free survival was found to be significantly prolonged in the IP approach compared to the intravenous route with median recurrent interval of 27.9 months and 22.2 months respectively (3). In addition, the IP arm had a longer overall survival of 63.2 months compared to 52.2 months in intravenous route chemotherapy (3). However, there are very limited evidences on a large volume disease (more than 1 cm in diameter) or palliative benefits. In one published series dealing with disease management found that patients who had even a single lesion of at least 1 cm in diameter has a poor clinical response rate of less than 10% (2).

Traditionally, IP chemotherapy is used in ovarian cancer mainly for the symptomatic relief of gross ascites. It has a better penetration to the tumour site with potential reduction of systemic absorption (4). The ideal technique, dosage, choice of agents and the duration of treatment are not very extensive reviewed in the randomized controlled trial and remained inconclusive. Largely its usage depends on the individual clinical experience.

Case Report

A 55-year-old, postmenopausal lady, para 3, first presented in July 2006 with acute abdomen with suspected twisted ovarian cyst and had an emergency staging laparotomy and right salpingo-oophorectomy with omentectomy following peritoneal washing. A complete debulking surgery was not able to achieve as it was difficult due to advanced tumour deposit with the left ovary adhered densely to the bowel and uterus. The histopathology examination confirmed serous cystadenocarcinoma of the ovary grade 3 with positive peritoneal washing and microscopic evidence of omental deposit.

Following surgery, she was commenced on three cycles of chemotherapy, combination of carboplatin and paclitaxel before undergoing a complete debulking surgery. Computed tomography of abdomen and pelvis following chemotherapy revealed a residual disease involving the contralateral ovary with suspected bowel involvement but non-significant nodal or liver metastasis. An optimal debulking surgery with hysterectomy, left salpingo-oophorectomy and pelvic nodes dissection was then performed with postoperative chemotherapy (carboplatin and paclitaxel) was administered. Biochemically, showed poor response of the treatment with persistently elevated CA125 level and CT scan of pelvis and abdomen revealed gross ascites with large pelvic mass measuring 6.2 cm by 6.5 cm by 5.4 cm appeared to be continuity with the ascites. A subcutaneous lesion measuring 2.1 cm by 1.2 cm seen at the right lower quadrant of the abdomen (Fig. 1). No pelvic adnaexal mass or enlarged paraaortic, inguinal or mesentrics nodes. No other abnormality of note. Following third cycles of carboplatin and paclitaxel, she was started on second line chemotherapy gemcitabin for two cycles as no clinical response. In fact, she required three episodes of peritoneal tapping to relief discomfort and respiratory embarrassment due to gross ascites.

Following discussion with patient, an intraperitoneal chemotherapy with cisplatin 50 mg was administered following abdominal tapping of two litres of straw colour ascites. The patient tolerated well with no apparent adverse effects. Two weeks later, abdominal distension had decreased, CA125 level reduced and she was very happy to complete three cycles of IP cisplatin. Amazingly, after the third course, she was asymptomatic for any tumour recurrence, no ascites dropped in CA125 significantly and a repeat CT scan of abdomen and pelvis revealed a significant improvement (Fig. 2).

Discussion

Intraperitoneal (IP) chemotherapy is not an extraordinary invention in the new era of management of ovarian cancer. It had been used extensively in the past not only in the small residual disease but also as palliative chemotherapy. However, to date, this modality is still remains an issue in term of its effectiveness, safety and selection of cases.

The illustrated case was outstandingly proven the effectiveness of IP chemotherapy (cisplatin) in the management of advanced ovarian cancer even with suboptimal cytoreduction or residual disease of more than 1 cm. More interestingly, a failed systemic intravenous chemotherapy using platinum based agent and paclitaxel followed by second line gemcitabin after no clinical response did not preclude benefits of intraperitoneal route. More so, extensive peritoneal disease found in this patient did not allay adequate distribution of the IP chemotherapy which was suggested by previous authors (7,8,9,10,11).

Although many studies addressed on the approach to reduce the risk associated with peritoneal cavity access including laparoscopic technique, and related issues on the type of catheters and when they should be inserted, yet this matter is still inconclusive (12). However, a

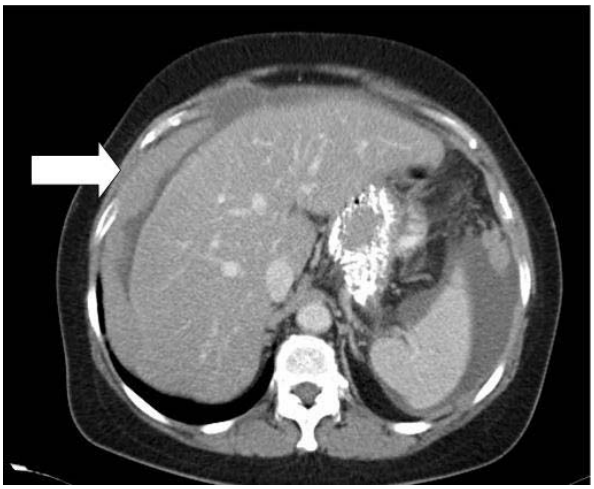

Figure 1: Axial contrast enhanced CT Abdomen shows multiple lobulated enhancing peritoneal masses anterior and lateral to the liver (white arrows). Presence of ascites also noted.

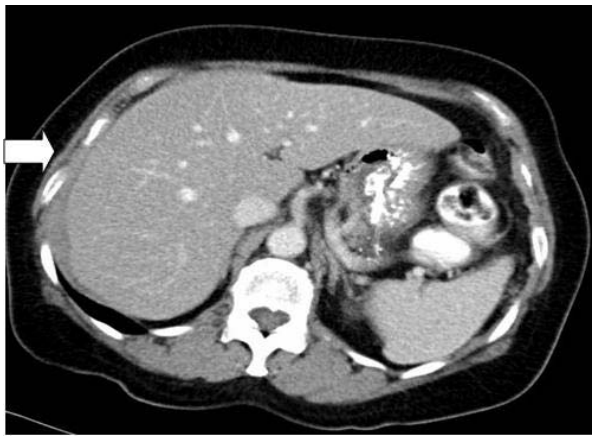

Figure 2: Follow up CT post-chemotherapy 4 months later, shows significant reduction in size of the peritoneal masses (white arrows) at the perihepatic area with minimal residual ascites.

simple large venous canulae sized 14 G placed under ultrasound guidance that we practiced in this case produced an excellent effect without any complications.

Previous large studies had demonstrated an optimal dose of 100 mg/m2 cisplatin every three weeks with excellent results (10,11,12). Further randomized controlled trial had attempted to evaluate the effect of 50-100 mg/m2 carboplatin with area under concentration versus time curve (AUC) 12 to AUC 6 and AUC 8 to AUC 4 respectively. Interestingly, all the findings demonstrated a comparable effect on progression-free disease and overall survivals (5). Even though the existing evident support various issues including therapeutic efficacy of IP, but it is still in conflict and difficult to justify that intraperitoneal cisplatin is superior than intravenous carboplatin (8,9,10,11).

Patients with malignant ascites are suggested to undergo drainage followed by IP installation of the chemotherapy. This basically for symptomatic relief of the distended abdomen added to further installation and maintaining desired concentration of the chemotherapy. More so, in this case who required multiple decompressions of the distended abdomen due to respiratory embarrassment and abdominal pain. Administration of IP exacerbates the development of intraabdominal adhesion making subsequent abdominal surgery more risky (13). In balancing the risk-benefits, proper assessment and discussion on the targeted issues need to be addressed to the patient.

There are reports suggesting the combination of intravenous chemotherapy (paclitaxel or docetaxel) followed by intraperitoneal route of platinum agents (cisplatin or carboplatin). The reason behind this is to delay the regional chemotherapy while the healing from cytoreductive surgery taking place. The result did not favor any specific approach as similar outcome had been observed. It is wise to consider the effective dose treatment and agents without creating any untoward effects to the patient. This patient had two courses of combination carboplatin and paclitaxel without any clinical response but amazingly, the disease had significantly improved following three cycles of IP cisplatin.

Based on this case and supported by other previous studies, it is clearly shown that IP chemotherapy works in the suboptimal debulking ovarian cancer. This study also revealed even in the unresponsive IV chemotherapy, IP route would be a good option.

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Conflict of interest

All authors are in agreement with no conflict of interest.

References

1. Chua TC, Baker B, Yan TD, Zhao J, Morris DL. Palliative effects of an incomplete cytoreduction

combined with perioperative intraperitoneal chemotherapy. Am J Clin Oncol 2010;33(6):568-71

2. Coven A, Carey M, Bryson P, et al. Systemic review of first line chemotherapy for newly diagnosed postoperative patients with stage 11, 111 or 1V epithelial ovarian cancer. Gynecol Oncol 2002; 85(1):71-80.

3. Markman M, Bundy BN, Alberts DS, et al. Phase 111 trials of standard intravenous cysplatin plus paclitaxel versus moderately high dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small volume stage 111 ovarian carcinoma. An intragroup study of the Gynaeco-Cooperative Oncology Group, Southwestern Oncology Group and Eastern Cooperative Oncology Group. J Clin Oncol 2001; 19(4):1001-7.

4. Dedrick RL, Flessner MF. Pharmacokinetic problems in peritoneal drug administration: tissue penetration and surface exposure. J Natl Cancer Inst 1997; 89(7):480-7.

5. Amstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006; 354(1):34-43.

6. Markman M, Reichman B, Hakes T, et al. Responses to second-line cisplatin-based intraperitoneal therapy in ovarian cancer: influence of a prior response to iintravenous cisplatin. J Clin Oncol 1991; 9(10):1801-5.

7. Lambert HE, Rustin GJ, Gregory WM, Nelstrop AE. A randomized trial of five versus eight courses of cisplatin of carboplatin in advance epithelail ovarian carcinoma: a North Thames Ovary Group Study. Ann Oncol 1997; 8(4):327-33.

8. Alberts DS, Green S, Hannigan EV, et al. Improve therapeutic index of carboplatin plus cyclophosphamide versus cisplatin plus cyclophosphamide: final report by the Southwest Oncology Group of a phase 111 randomized trial in stages 111 and 1V ovarian cancer. J Clin Oncol 1992; 10(5):706-17.

9. Swenerton K, Jeffrey J, Stuart G, et al. Cysplatin-cyclophosphamide versus carboplatin-cyclophosphamide in advanced ovarian cancer: a randomized phase 111 study of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1992; 10(5):718-26.

10. duBois A, Luck HJ, Meier W, et al. A randomized clinical trial of cisplatin/ paclitaxel versus carboplatin/ paclitaxel as first line treatment of ovarian cancer. J Natl Cancer Inst 2003; 95(17):1320-9.

11. Ozols RF, Bundy BN, Greer BE, et al. Phase 111 trial of carboplatin and paclitaxel compared to cisplatin and paclitaxel in patients with optimally resected stage 111 ovarian cancer. A Gynaecologic Oncology Group study. J Clin Oncol 2003; 21(17):3194-200.

12. Walker JL, Amstrong D, Huang HQ, et al. Intraperitoneal catheter outcomes in a phase 111 trial of intravenous versus intraperitoneal chemotherapy in optimal stage 111 ovarian and primary peritoneal cancer. A Gynecologic Oncologic Group study. Gynecol Oncol 2006;100(1):27-32.

13. Lopez JA, Krikorian JG, Reich S, et al. Clinical pharmacology of intraperitoneal cisplatin. Gynecol Oncol 1985; 20(1):1-9.