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SHORT COMMUNICATION

Complete remission of platinium refractory ovarian cancer with second line tegafur with uracil monotherapy: a case report

Celalettin Camci · Alper Sevinc · Yilmaz Aslan · Mehmet Emin Kalender · Suleyman Buyukberber

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Abstract
Background Ovarian cancer remains one of the most lethal of all gynecologic malignancies, accounting for more deaths than cervical and uterine cancer combined. Advanced ovarian cancer is a chemosensitive tumor and most patients initially respond to platinum-based combination chemotherapy with response rates of about 70%, including a high proportion of complete responses. However, despite aggressive surgery and chemotherapy, more than 80% of patients will relapse and will then be treated with second line chemotherapy with objective responses in about 20% of patients and even lower percentages of complete responses.
Case We observed a 42-months of complete response with administration of 1-[2-tetrahydrofuryl]-5-fluorouracil mixed with uracil (UFT) in patient with platinium refractory ovarian cancer.
Conclusion We report a complete remission of platinium refractory epitelial ovarian cancer with UFT monotherapy that was not reported previously.

Keywords Ovarian cancer · Complete remission · Tegafur with uracil

C. Camci · A. Sevinc · M. E. Kalender
Department of Medical Oncology,
Gaziantep Oncology Hospital, School of Medicine,
Gaziantep University, Gaziantep 27310, Turkey

Y. Aslan (✉)
Department of Internal Medicine, School of Medicine,
Gaziantep University, Gaziantep 27310, Turkey
e-mail: sauronmd@yahoo.com

S. Buyukberber
Department of Medical Oncology, School of Medicine,
Gazi University, Ankara, Turkey

Introduction

Ovarian cancer is the most common cause of death among women with gynecologic malignancies, and the fourth leading cause of cancer death in women in the United States [1]. Therapy for newly diagnosed epithelial ovarian cancer (EOC) is determined primarily by the extent of the disease at the time of diagnosis, as expressed in the International Federation of Gynecology and Obstetrics (FIGO) staging system. Approximately 75% of women present with stage III (disease that has spread throughout the peritoneal cavity or that involves paraaortic or inguinal lymph nodes) or IV disease. The standard of care for those patients is maximal surgical cytoreduction followed by systemic chemotherapy [2]. However, despite aggressive surgery and chemotherapy, more than 80% of patients will relapse and will then be treated with second line chemotherapy with objective responses in about 20% of patients and even lower percentages of complete responses [3]. Successful management of platinum-resistant epithelial ovarian cancer requires the use of non-cross resistant agents. Single agent therapy is usually chosen. Although combination regimens are associated with somewhat higher objective response rates and a 2–3 month improvement in progression-free survival, they are also more toxic, and no regimen has produced a survival benefit compared to single agent therapy. However, women with an asymptomatic recurrence do not necessarily all require immediate treatment. Women with recurrent disease are unlikely to be cured of their disease even with aggressive treatment. Thus, the goal of salvage therapy is palliation, not cure resulting from long-term remission (which can only occasionally be achieved). This is an important concept and should be clearly understood by the patient and family at the onset of treatment [4].

Several chemotherapeutic regimens have been used as single agents in phase II trials with patients previously treated with cisplatin including paclitaxel, topotecan, liposomal doxorubicin, gemcitabine and oxaliplatin, showing objective response rates ranging from 10 to 50% and different toxicity profiles [5].

Early clinical trials of UFT were conducted in Japan [6], where it has been licensed for use since 1983 and has been used to treat a variety of solid tumours. UFT is a combination of two chemotherapy drugs: tegafur and uracil. Tegafur is a prodrug of fluorouracil and the addition of uracil inhibits the degradation of fluorouracil [7].

Herein we report a complete remission of platinium refractory epitelial ovarian cancer with UFT monotherapy that was not reported previously.

Case report

A 60-year-old woman presented with complaint of increasing abdominal girth. Computed tomography (CT) showed a 6 × 4 cm right pelvic tumor, with both cystic and solid components and ascites. Her initial CA-125 was 374 U/mL (normal range, <35 U/mL). Cytopathological examination of ascites revealed malignant cells. An exploratory laparotomy was performed. Total hysterectomy, bilateral salpingo-oophorectomy, and partial omentectomy were performed. Final staging and pathology was consistent with papillary serous adenocarcinoma of the ovary, FIGO stage IIIC. Postoperative CA-125 level was decreased to 34 U/mL after. Postoperatively, the patient received front-line standard carboplatin (AUC 6) and paclitaxel (175 mg/m^2) chemotherapy for a total of four cycles. After the fourth cycle of chemotherapy her CA-125 was elevated to 354 U/mL. CT scans of the abdomen and pelvis revealed a large left pelvic mass of 5.0 × 5.5 cm, and right pelvic mass of 2 × 2.5 cm with both cystic and solid components which was consistent with recurrence. Multiple noduler masses in the left kidney were also identified. There was no CT evidence of ascites. The patient was diagnosed as platinium refractory ovarian cancer and her chemotherapy was changed. Six cycles of UFT 400 mg/day as a second line chemoterapy was administered at monthly intervals. Following completion of 6 cycles of chemotherapy, serum CA 125 level recorded was 14.7 U/mL. Follow-up of abdominal and pelvic CT at the end of the chemotherapy showed no evidence of recurrent or residual lesion in the pelvis and abdomen. Additionally, no free fluid or lymphadenopathy was demonstrated. Chemotherapy was completed to twelve cycles with complete response. Fourty-two months later, the patient was seen in our clinic with complaint of headache. A possible cranial metastasis of ovarian cancer was suspected. Cranial MRI showed 2 × 2 cm intracranial solid hypodense lesion. An complete excisional biopsy showed metastatic ovarian carcinoma. She received cranial radiotherapy. Serum CA 125 level was 18.4 U/ml and there was no evidence of recurrence at physical examination and/or abdomino-pelvic computed tomographies. The patient is still in remission for another 18 months.

Discussion

A number of factors are associated with a greater likelihood of disease relapse or persistence after first-line therapy of ovarian cancer. The most important predictors of relapse and the need for salvage or second-line therapy are clinical stage and bulk of disease after surgery. Advanced age also represents a risk factor for relapse [2, 8]. The importance of age was demonstrated in a series of 624 women with invasive EOC who were treated with platinum-based chemotherapy. The 5-year-survival rates for women under 40 years old, and older women were 65 and 20%, respectively [8]. Our patient was 60 years old and FIGO stage IIIC.

The selection of salvage therapy is commonly based upon whether women are “sensitive” or “resistant” to initial platinum-based treatment. Patients who respond to initial platinum-based therapy and have a significant relapse-free interval (more than 6 months) have a high probability of responding again to platinum-based treatment at the time of relapse. These patients are termed “platinum-sensitive”. The length of the prior response is highly predictive of the upper limit of the duration of disease control that can be expected with second-line cisplatin-based chemotherapy [9]. Patients with platinum-resistant disease do not generally respond to second-line platinum-based therapy. They have a poorer prognosis, and should be considered for salvage therapy with non-cross-resistant agents.

Recurrent EOC may be suspected by the development of new symptoms, the radiographic detection of an asymptomatic disease recurrence by CT scans, or a rising serum concentration of the tumor marker CA-125, which may predate radiographic disease progression by up to 6 months [10, 11]. Formal definitions of ovarian cancer progression according to both clinical and CA 125 criteria have been proposed [11, 12]. However, asymptomatic increased serum CA-125 concentration should be interpreted with caution as it can be encountered in several benign conditions [13–19].

The combination of 5-fluorouracil (5-FU) plus leucovorin (each given daily for 5 days every 4 weeks) was studied by the Gynecologic Oncology Group. Among 29 patients with platinum-resistant disease, one complete response and 4 partial responses were noted (response rate 17%); however, among 15 patients with platinum-sensitive disease, only one responded (7%) [20].

Ohwada et al. made a comparative study on postoperative supplementary chemotherapy including UFT and FT-E for gynecological malignant tumors. The number of cases registered totaled 182, which was grouped into ovarian cancer (53 cases), uterine cervical cancer (89 cases) and endometrial cancer (30 cases). Completed cases among them consisted of ovarian cancer (53 cases), uterine cervical cancer (86 cases) and endometrial cancer (27 cases) for a total of 166 cases. Ovarian cancer was stratified into the completely and incompletely removed cases, uterine cervical cancer into postoperative non-irradiated and irradiated cases and endometrial cancer into the positive metastasis (+) group and negative metastasis (−) group. Then the UFT administration group and FT-E administration group were compared for postoperative survival. There were control groups for both ovarian and endometrial cancer. UFT administration showed a significant improvement in the survival rate ($P < 0.05$) compared to the FT-E administration group in the cases of ovarian cancer completely removed and the cases of endometrial cancer irradiated after operation. No significant difference was observed between other groups compared [21]. Secondly, Chen et al. studied twenty nine patients with ovarian cancer of common epithelial origin who had no evidence of disease proved by CT after the initial operation and chemotherapy. The patients were randomized into two groups; (1) administration of UFT orally at a daily dose of 300 mg 484.3 ± 154 days, 12 cases, (2) no further therapy, 17 cases. No significant difference of recurrence ratio was observed between the two groups [22]. In a third study, Tanaka et al. used single oral UFT in 17 ovarian carcinoma patient in a phase II study. Two PR cases were observed out of 13 cases for a rate of 15.4%. Side-effects were detected in 10 of the cases (58.8%) mainly anorexia (17.6%), stomatitis (17.8%), nausea/vomiting (11.8%), leukopenia (11.8%) and thrombocytopenia (11.8%) [23].

In the English literature, there were no reports on usage of UFT in platinium refractory ovarian cancer patients. We observed a 42-months complete response with administration of a single oral drug. In conclusion, a single case is not enough to change practice but may be enough to consider further investigation and a call for further studies is justified.

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