Clinics of Oncology

Case Report

ISSN: 2640-1037 |Volume 6

An Outpatient, Platinum-Free, Oral Arsenic Chemotherapy Modality for Advanced Recurrent Epithelial Ovarian Cancer: A Report of Two Cases

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Received: 08 May 2022
Accepted: 30 May 2022
Published: 04 Jun 2022
J Short Name: COO

Citation:

Xiao-Ping Li, An Outpatient, Platinum-Free, Oral Arsenic Chemotherapy Modality for Advanced Recurrent Epithelial Ovarian Cancer: A Report of Two Cases. Clin Onco. 2022; 6(7): 1-6

Keywords:

Ovarian neoplasms; Recurrent carcinoma; Ovarian epithelial; Oral arsenic com pounds; Chemotherapy

1. Abstract

Recurrent epithelial ovarian cancer is generally associated with platinum resistance and poor prognosis. Although there are many single-drug chemotherapy regimens, the response rate is low. The development of new antineoplastic drugs and new chemotherapy modalities for recurrent epithelial ovarian cancer therapy has become a major focus of gynecological oncologists. One oral arsenic compound, the Realgar-Indigo naturalis formula (RIF), has unique antitumor mechanisms that include induction of apoptosis and inhibition of blood vessel growth. Here, we are the first to report the cases of two patients who received an oral arsenic-containing RIF treatment regimen for 4 weeks (25 mg/kg body weight per day) followed by 4 weeks of rest. The results showed that the oral commercial arsenic RIF treatment protocol was highly effective for the treatment of recurrent epithelial ovarian cancer, which could prolong the platinum-free and overall survival intervals. This regimen is expected to become a new oral antineoplastic drug for outpatient chemotherapy for recurrent epithelial ovarian cancer because of the convenience of its use, good patient quality of life, and high cost-effectiveness. However, larger sample, randomized controlled clinical trials are needed.

2. Introduction

Epithelial ovarian cancer is a lethal gynecological cancer worldwide. After initial surgery and adjuvant chemotherapy, approximately 70-80% of patients relapse, typically due to the development of platinum resistance, and the 5-year median overall survival rate for epithelial ovarian cancer is less than 40%1-3. For platinum-resistant recurrent epithelial ovarian cancer, the monotherapy regimen recommended by the National Comprehensive Cancer Network includes pegylated liposomal doxorubicin and paclitaxel-albumin, but the efficacy rate is low. Therefore, it is important to prevent platinum resistance, prolong the time to platinum resistance development, and identify new drugs to treat drug-resistant recurrent epithelial ovarian cancer patients. Two arsenic compounds have been developed, intravenous arsenic trioxide and an oral arsenic compound named Realgar-Indigo naturalis formula(RIF), which is an oral-containing arsenic tablet (mainly containing tetra-arsenic tetra-sulfide compound, As4S4, and arsenic disulfide, As2S2; Fufang Huangdai tablet, Tianchang Yifan Pharmaceutical Co., Ltd). RIF is the only commercially available oral arsenic agent, and has been used clinically since 2009; RIF has unique antitumor mechanisms, including inhibition of anti-apoptotic factors and blood vessel growth. Basic studies have been performed on the effect of RIF on platinum-sensitive and platinum-resistant ovarian cancer cells, and the results showed that RIF exerts its antitumor effect through multiple pathways, such as inducing apoptosis via Bcl-2/Bax, blocking angiogenesis, and inhibiting DNA synthesis [1-5]. In the clinic, the results of a multicenter noninferiority, randomized controlled phase 3 clinical trial showed that RIF achieved good effects in malignant tumors, such as acute promyelocytic leukemia and several solid tumors [6-10]. The oral arsenic RIF regimen provides similar efficacy to intravenous arsenic trioxide in acute promyelocytic leukemia, and has the advantages of high efficiency, cost-effectiveness, convenience, and good patient quality of life [11,12]. We expected that oral commercial

arsenic RIF could be used to establish an outpatient chemotherapy modality for recurrent epithelial ovarian cancer, although the efficacy and safety of RIF for the treatment of recurrent epithelial ovarian cancer remains to be confirmed. Here, we describe the first successful treatment of two patients with advanced relapsed epithelial ovarian cancer with the oral arsenic RIF regimen.

3. Case Presentation

3.1. Case 1

A 72-year-old female presented with asphyxia and fatigue. Chest computed tomography and hydrothorax cytology showed malignant cells, which were considered to be metastases of malignant tumors of the genital tract. Abdominal computed tomography imaging showed that the ovarian malignant tumors were complicated with omental and pelvic peritoneal metastases. Pelvic magnetic resonance imaging showed a 2.0 × 3.6 cm mass, and the signal characteristics were consistent with those of malignant tumors. The level of serum cancer antigen 125 (CA125) was increased to 1457.00 U/mL, and the level of serum cancer antigen 153 was increased to 300.00 U/mL. The patient then underwent preoperative laparoscopy, and histopathological evaluation of the peritoneal biopsy revealed invasive epithelial ovarian cancer. After multidisciplinary consultation, the patient received 4 cycles of neoadjuvant chemotherapy with paclitaxel combined with carboplatinum. Then, she underwent primary cytoreduction surgery, including total hysterectomy, bilateral salpingo-oophorectomy, gross omentum resection, abdominal lymph node resection and pelvic lymph node radical resection, on January 2015. There were no visible residual diseases (R0). The final histological examination confirmed that the patient's tumor was high-grade serous ovarian cancer at FIGO Stage IV. Immunohistochemical analysis showed that the tumor was CK7 (+), ER (+), PR (-), PAX-8 (+), P53 (+), and Ki67 (+, 50%). The patient received combination chemotherapy comprising paclitaxel and carboplatinum in 4-weekly cycles for a total of eight cycles until August 2015 and achieved complete remission. During regular outpatient follow-up, on October 21, 2016, a pelvic ultrasound revealed that the disease had relapsed, and a new mass (2.1 cm × 1.9 cm × 1.6 cm) posterior to the vaginal residue was diagnosed as relapsed epithelial ovarian cancer. The patient then received two cycles of adjuvant chemotherapy with the TC regimen. Due to the gradual increase in the vaginal stump mass (2.5 cm × 1.9 cm × 2.5 cm), the chemotherapy regimen was changed, and the patient received 4 cycles of an IAP (isophosphamide, oxaliplatin and epirubicin) combined regimen from March 3, 2017 to July 3, 2017. Sequential chemotherapy was 3 cycles of combined chemotherapy (Taxotere and irinotecan) from July 31, 2017 to October 10, 2017. According to the response evaluation criteria in solid tumors (RECIST), the chemotherapy efficacy was CR. After 5 months of follow-up, a new mass (1.8 cm × 1.1 cm × 1.2 cm) at the posterior of the vaginal residue was found, and the patient was again diagnosed with recurrent epithelial ovarian cancer. At that time, the patient could not tolerate cytotoxic chemotherapy, and she refused to receive intravenous chemotherapy. After being fully informed of the procedure involved, the patient signed an informed consent form and chose to take the oral arsenic RIF regimen. The regimen consisted of intermittent oral arsenic RIF therapy for 4 weeks (compound Huangdai tablet, 25 mg/kg bodyweight daily) followed by 4 weeks of rest, with a total of 8 cycles over 15 months. Figure 1 shows the size of the pelvic neoplastic mass during administration of the oral arsenic RIF regimen. Figure 2 shows the changes in CA125 levels observed during the administration of the oral arsenic RIF regimen. Major side effects included nausea, vomiting, diarrhea, upper abdominal pain, mucositis and rash, which did not necessitate discontinuation of the treatment. In May 2019, the patient's pelvic mass increased gradually (3.6 cm × 5.3 cm × 3.2 cm by transvaginal ultrasound), and the serum cancer antigen 125 level increased to 165.90 U/mL; with the informed consent of the patient, we performed the optimal secondary cytoreduction surgery, with no visible residual disease (R0). The pathology was confirmed to be high-grade serous ovarian cancer in the rectal specimens. Subsequently, the patient received 5 cycles of a chemotherapy regimen with albumin paclitaxel combined with oxaliplatin from June to September 2019 and 2 cycles of IAP intravenous injection from October to November 2019. The patient's serum cancer antigen 125 level then decreased to the normal range. The course of chemotherapy was uneventful with few side effects, and the patient remained in good condition and was still alive at the time of writing.

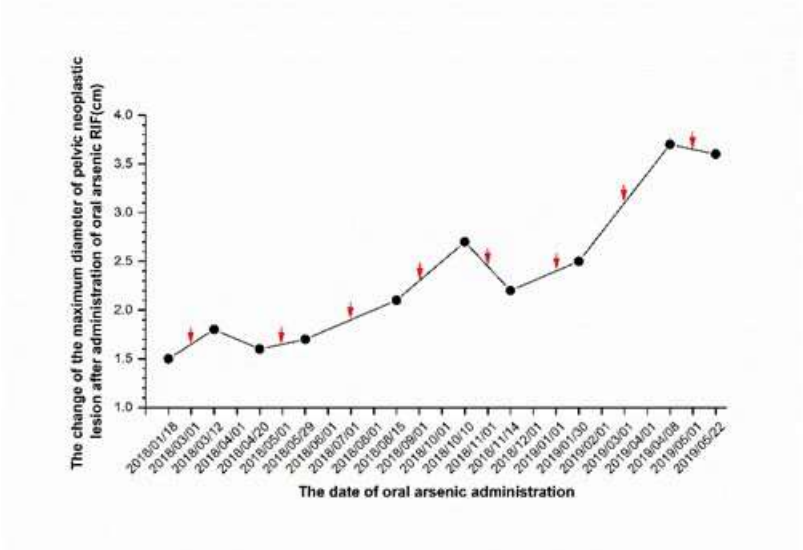

Figure 1: The change in the maximum diameter of the pelvic neoplastic lesions after administration of oral arsenic in patient 1. Arrows indicate the start of oral arsenic administration.

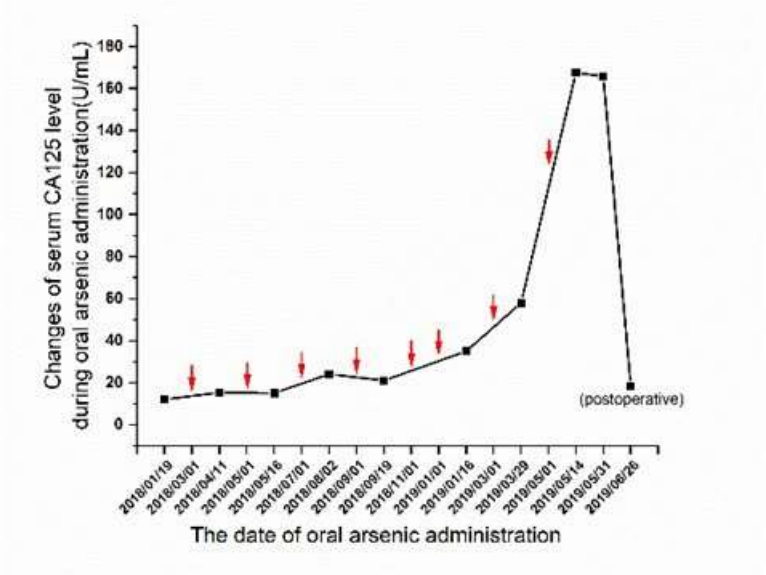

Figure 2: Changes in serum CA125 levels during administration of oral arsenic RIF in patient 1. Arrows indicate the start of oral arsenic administration.

3.2. Case 2

A 69-year-old female presented with intermittent pain in the left lower abdomen for 1 month. Transvaginal sonography showed an uneven echo mass of 8.9 ×7.7 ×7.3 cm in the left uterine appendage. Abdominal computed tomography imaging showed peritoneal and greater omentum metastases with large lesions. Pelvic magnetic resonance imaging showed a right ovarian mass, with local intestinal adhesion and posterior peritoneal diffuse thickening. The patient underwent laparotomy for the ovarian tumor in May 2016. Intraoperative exploration revealed that the left ovarian mass was 8 cm × 6 cm × 6 cm, and the peritoneal bladder, Douglas' pouch and peritoneal surface were covered with diffuse thin lamellar lesions. The omentum was infiltrated with an 8 cm × 7 cm x 2 cm tumor mass adhered to the left abdominal wall, and the peritoneum of the descending colonic groove showed an 8 cm × 5 cm × 5 cm lesion involving the intestinal serosa. The surgical procedures included total abdominal hysterectomy, bilateral salpingectomy, total omentectomy, pelvic and abdominal aortic pelvic lymph node dissection, intraperitoneal infusion chemotherapy (cisplatin 80 mg), and no visible residual disease was present (R0). The immunohistochemical staining results were CK7 (+), CK20 (-), PAX-8 (+), ER (70% +), PR (-), P53 (+), p16 (+), WT1 (+), vimentin (-), and Ki-67 (50% +). Pathological examination confirmed that the tumor was high-grade serous ovarian cancer, and the FIGO stage was IIIC. Since May 30, 2016, the patient received 8 cycles of intraperitoneal and/or intravenous combination chemotherapy with the TC regimen. The last chemotherapy was on February 10, 2017. The efficacy of chemotherapy was complete remission as evaluated by the RECIST. After eight months of follow-up, the serum CA125 level increased gradually from 35 to 103 U/mL,

while computed tomography imaging showed that there were several small lymph nodes in the retroperitoneum. On October 17, 2017, we diagnosed a biochemical relapse. Although the patient was platinum-sensitive, after undergoing multiple chemotherapy cycles, she experienced serious side effects, which affected her quality of life. The patient was unwilling to continue chemotherapy and felt very anxious. After full informed consent was obtained from the patient, the patient signed a consent form to receive the oral arsenic RIF regimen. The regimen consisted of oral arsenic RIF for 4 weeks (compound Huangdai tablet, 25 mg/kg bodyweight per day) followed by a 4-week rest every cycle, which was initiated on March 7, 2018. The cancer antigen 125 serum level decreased during oral administration of arsenic until October 2019, and the serum CA125 value increased to 164.6 U/mL; however, the CA125 value increased in a wave pattern after every cycle of RIF, and the level decreased when RIF was resumed. Therefore, the patient continued take the oral arsenic RIF regimen. On September 24, 2020, the serum CA125 level increased to 256.8 U/mL, and after obtaining patient consent, the regimen was combined with apatinib mesylate tablets from October 28, 2020. During administration of the oral arsenic RIF regimen, the changes in cancer antigen 125 serum levels decreased again, as shown in Figure 3. The change in the maximum diameter of the pelvic lymph nodes is shown in Table 1. The patient continues to take oral arsenic RIF, remains in good condition, and is alive at the time of writing. As in Case 1, the main side effects included nausea, vomiting, diarrhea, upper abdominal pain, mucositis, and rash, none of which required suspension of RIF therapy.

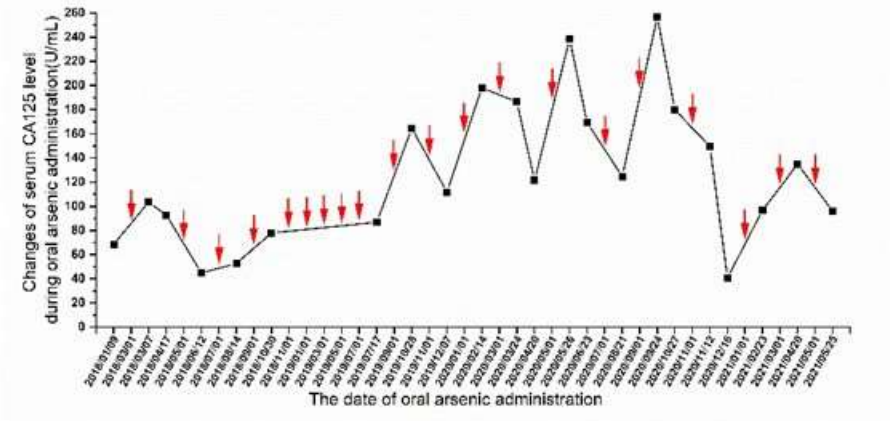

Figure 3: Changes in serum CA125 levels during administration of oral arsenic RIF in patient 2. Arrows indicate the start of oral arsenic administration.

Table 1: The change in the maximum diameter of the pelvic lymph nodes after administration of oral arsenic in patient 2.

Date	2019.10	2020.5	2021.5
Mass(cm)	1.2	1.5	0.9

4. Discussion and Conclusions

In this manuscript, we reported the first successful treatment with traditional Chinese medicine oral arsenic tablets of advanced recurrent platinum-sensitive or platinum-resistant epithelial ovarian cancer, and the prognosis of the latter was good. Although the monotherapy regimen recommended by the National Comprehensive Cancer Network includes pegylated liposomal doxorubicin, different paclitaxel regimens, gemcitabine or oral etoposide, the response rate to these drugs is low (< 30%). New antineoplastic drugs, especially for oral administration, have become the focus of gynecological oncologists [13]. There are two kinds of arsenic compounds, intravenous arsenic trioxide and an oral arsenic compound, the Realgar-Indigo naturalis formula (RIF), an arsenic-containing tablet (mainly including tetra-arsenic tetra-sulfide, As4S4 and As2S2). Intravenous arsenic trioxide has been used to treat malignant tumors, including promyelocytic leukemia, hepatocellular carcinoma, bladder cancer, and liver cancer 10. Arsenic trioxide alone or combined therapy with arsenic trioxide has been found to be effective for the treatment of promyelocytic leukemia. In clinical trials, the combination of all-trans retinoic acid and arsenic trioxide resulted in a CR in 90% to 100% of APL patients, with an overall survival rate of 86% to 97%. In our department, Arsenic trioxide has been found to be an effective treatment for endometrial cancer6. The oral arsenic-containing compound RIF has been applied clinically since 2009 and has been shown to be effective for the treatment of adult APL; RIF is the only oral arsenic agent that is commercially available. Oral RIF was not inferior to intravenous arsenic trioxide for the treatment of patients with non-high-risk acute promyelocytic leukemia in an international multicenter, randomized phase 3 clinical trial and has the advantages of high efficacy, cost-effectiveness, convenience and good postoperative patient quality of life, leading to significant improvements in treatment and the establishment of an outpatient nonchemotherapeutic treatment regimen for APL [11,12]. Howev-

er, to date, few studies have been conducted on the oral arsenic RIF regimen for the treatment of patients with ovarian cancer and recurrent epithelial ovarian cancer. Here, we report the first two cases of patients with recurrent epithelial ovarian cancer treated with oral arsenic. Patient 1 experienced relapse and developed clinical drug resistance after primary cytoreduction surgery and platinum-based combined chemotherapy regimens. RIF treatment provided the patient with a platinum-free interval of 15 months, followed by optimal secondary cytoreduction surgery (R0) and 7 cycles of platinum-based combined chemotherapy. To date, the patient's serum CA125 level has remained decreased and in the normal range. During the period of oral arsenic therapy, the patient remained in a good condition and experienced few side effects. Patient 2 experienced biochemically relapsed ovarian cancer after primary cytoreduction surgery and paclitaxel and carboplatin combined chemotherapy regimens, and received the same oral arsenic therapy as patient 1. This patient also achieved a long-term platinum-free interval of over 39 months with few side effects and was followed up with until the time of writing; she remained in good health. In this paper, we provide clinical data showing that monotherapy with RIF had high efficacy in patients with relapsed ovarian cancer, and the results show that RIF has significant therapeutic effects on patients with recurrent ovarian cancer and plays a positive role in prolonging patient survival times and improving quality of life. In addition, RIF has few side effects. Our results suggest that RIF can be used as a maintenance therapy for patients with recurrent ovarian cancer and may restore platinum sensitivity and improve the survival rate [14]. The oral arsenic RIF chemotherapy regimen may be an effective outpatient treatment for recurrent epithelial ovarian cancer. What is the antitumor mechanism of the oral arsenic preparation? The mechanism may predominantly involve the induction of apoptosis and inhibition of cancer cell proliferation [15]. Realgar is the main component of RIF, which has antibacterial, antiviral and anti-inflammatory effects. Studies have shown that Realgar contains tetra-arsenic tetrasulfide and As2S2, which could inhibit proliferation and induce apoptosis in K562 and K562/ADM cell lines, which may be related to the upregulation of MDR1 mRNA expression and downregulation of P-glycoprotein expression induced by Realgar [16]. The analysis of the bioavailability of realgar nanoparticles prepared by cryo-grinding in vitro and in vivo showed that the nanoparticles had an anti-proliferative effect and induced typical apoptosis effects in ovarian cancer cells (CI80-13S, OVCAR OVCAR-3) and cervical cells (HeLa) [17]. As4S4 may inhibit proliferation and induce apoptosis in HeLa cervical cancer cells by significantly inhibiting the expression of cyclooxygenase-2 and the release of prostaglandin E2 [18]. As4S4 could also suppress the growth of implanted ovarian carcinoma cells in nude mice and induce tumor cell apoptosis. The antitumor activities of As4S4 may be related to apoptosis induced by changes in the expression of Bcl-2/Bax 4. As2S2 can inhibit the proliferation of a DDP-resistant ovarian cancer cell line (C13K) and induce cell apoptosis, which may be related to BCL-2 or AKT expression downregulation and BAX expression upregulation5. Another study showed that arsenic compounds combined with cisplatin had synergistic effects on paclitaxel-resistant and cisplatin-resistant ovarian cancer lines [19,20]. These results suggest that arsenic compounds combined with chemotherapy may act on recurrent epithelial ovarian cancer cells through different mechanisms. The toxicity of oral arsenic-containing drugs has attracted the attention of researchers and includes side effect such as leukocytosis, syndrome differentiation, hepatotoxicity, diarrhea, and a prolonged QTc interval. However, studies have shown that a cumulative dose of approximately 1500 mg of arsenic trioxide and even 63,000 mg of arsenic trioxide did not cause either mild or severe adverse reactions [11], while no cumulative dose effects for oral arsenic RIF have been reported. These two case report results suggest that the RIF monotherapy regimen is effective for recurrent epithelial ovarian cancer, and combined therapy may be effective, which suggests that RIF could be used for maintenance therapy for primary or recurrent epithelial ovarian cancer in the future, leading to prolonged disease-free survival times and a delay in disease recurrence. At present, polyadenosine diphosphate ribose polymerase inhibitors have been used for maintenance therapy for first-line or platinum-sensitive recurrent ovarian cancer [21]. However, this approach involves several side effects and is expensive. We recommend RIF as a maintenance therapy due to its positive effects, minimal side effects, reduced expense, convenience of oral administration, and good resulting patient quality of life. Currently, a single-center clinical study is in progress in our department that is investigating RIF as a new maintenance therapy for relapsed ovarian cancer. In summary, the results obtained from the two patient cases reported demonstrate clinical benefits and lower side effects with the oral commercial arsenic RIF regimen, indicating that the RIF regimen may be safely used in an outpatient setting, thus reducing hospitalization cost, increasing convenience and improving patient quality of life; thus, RIF may become a new option for outpatient chemotherapy for recurrent epithelial ovarian cancer. Large-sample, randomized controlled, multi-centric and larger clinical trials are needed to verify this finding.

6. Acknowledgments

This study was supported by the National Key R&D program of China (2016YFC1303100, 2016YFC1303103).

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