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Case Series

Stage IV ovarian cancer cured 10 yrs after oral metronomic chemotherapy with etoposide and tamoxifen

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Abstract

Ovarian cancer remains one of the leading causes of gynecological cancer mortality, with most patients presenting at advanced stages and facing poor prognosis. While conventional chemotherapy forms the backbone of treatment, it is often associated with significant adverse effects and suboptimal cure rates. Metronomic chemotherapy, characterized by frequent administration of lower doses of chemotherapeutic agents, has emerged as a promising alternative strategy. This approach potentially offers reduced toxicity while maintaining therapeutic efficacy through continuous drug exposure and anti-angiogenic effects. We present a series of four cases of advanced ovarian cancer treated with metronomic chemotherapy using tamoxifen and etoposide. The patients, aged 39-65 years, achieved complete remission and maintained disease-free status during long-term follow-up ranging from 5-10 years, as confirmed by serial CA-125 measurements and imaging studies. These cases demonstrate the potential utility of metronomic chemotherapy as a viable treatment option in advanced ovarian cancer, particularly in resource-limited settings. Our findings contribute to the growing evidence supporting the role of metronomic chemotherapy in gynecological oncology and warrant further investigation through larger, prospective studies.

Keywords: Ovarian cancer, Chemotherapy, Tamoxifen, Etoposide

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1. Introduction

Ovarian cancer is the seventh most common cancer among women, accounting for about 4% of all cancers associated with females, with a mortality ranging between 3.2-4.3 per 100,000.[1] In general, the five-year survival rate for ovarian cancer remains at 50.9%.[2] The disease is particularly challenging due to its insidious onset and non-specific symptoms, leading to delayed diagnosis. Most patients are diagnosed at an advanced stage (III or IV), which is associated with poor survival (5-year survival is 27% for stage III and 13% for stage IV).[3]

Despite advances in treatment modalities, the prognosis remains poor. Even with chemotherapy, most patients (58%) were observed with distant metastasis and nearly 43% of patients had disease worsening during the 5-year follow-up.[4] The standard treatment of ovarian cancer usually involves cytoreductive surgery, with or without intraperitoneal and intravenous chemotherapy.[5] The therapeutic arsenal includes several chemotherapeutic drugs, typically used in combinations of topoisomerase inhibitors, selective estrogen receptor antagonists, and antitumor antibiotics, along with monoclonal antibodies as a part of targeted therapy.[6] However, patients receiving traditional chemotherapy face numerous adverse effects such as nausea, vomiting, hair loss, cognitive dysfunction, fatigue, changes in sexual functioning, and reductions in quality-of-life ratings.[7] These side effects often lead to treatment discontinuation or dose reduction, potentially compromising therapeutic outcomes.

Several strategies are being explored for optimizing the therapeutic effects of antineoplastic chemotherapy while minimizing their adverse effects. One promising approach is metronomic chemotherapy, which involves frequent administration of conventional chemotherapeutic agents at very low doses. This strategy offers potential advantages of

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minimizing adverse effects, improving anticancer response, and reducing the chances of developing acquired drug resistance.[8] The biological basis of metronomic chemotherapy lies in its anti-angiogenic properties and its ability to target both cancer cells and their supportive microenvironment. Furthermore, these regimens have been shown to stimulate the endogenous immune system in efficiently targeting cancer cells,[9] representing a more holistic approach to cancer treatment.

The economic implications of metronomic chemotherapy are particularly relevant in the current healthcare landscape. The use of low doses of expensive chemotherapeutic drugs facilitates the availability of these drugs for a wider population, particularly in developing nations with resource-constrained healthcare systems. This cost-effectiveness, combined with potentially better tolerability, makes metronomic chemotherapy an attractive treatment option worthy of further investigation.

Considering the dearth of literature regarding the utility of metronomic chemotherapy, particularly in ovarian cancer, we present here a series of cases where metronomic chemotherapy was observed to be efficacious in providing cure in patients with ovarian cancer. These cases not only demonstrate the potential therapeutic benefits but also provide insights into the practical implementation of metronomic chemotherapy protocols in clinical practice.

2. Case 1

A 65-year-old female presented in October 2013 with increased stool frequency and abdominal pain. CT scan revealed massive ascites, a 10-12 cm pelvic mass, multiple peritoneal deposits, and pleural effusion. Ascitic fluid analysis was performed at the previous hospital for diagnostic and therapeutic evaluation. Following the diagnosis of postmenopausal ovarian cancer in October 2013, the patient received two cycles of chemotherapy before undergoing total abdominal hysterectomy (TAH) with bilateral salpingo-oophorectomy (BSO), omentectomy, and debulking. A right hemicolectomy with anastomosis was also performed. Tissue microarray analysis was conducted to guide ongoing management. Post-operatively, the patient completed six cycles of chemotherapy, followed by oral metronomic chemotherapy with etoposide and tamoxifen. Regular follow-up continued over a 10-year period until October 2024. Serial C.A. 125 measurements confirmed complete remission while maintaining oral metronomic chemotherapy.

3. Case 2

A 43-year-old female presented in August 2013 with abdominal pain. Initial CT scan demonstrated omental thickening and bilateral adnexal masses. Diagnostic evaluation of pleural fluid and elevated CA-125 led to the diagnosis of epithelial ovarian carcinoma in September 2013. The patient received nine cycles of oral metronomic chemotherapy with etoposide and tamoxifen before undergoing TAH with BSO. This was followed by nine additional cycles of the same metronomic regimen. Post-surgical histopathology revealed right ovarian endometriosis with endometriotic cyst, while the left ovarian mass showed complete tumor necrosis with foreign body giant cell reaction. Following the discontinuation of metronomic therapy, the patient underwent biannual follow-ups for five years, followed by annual reviews for the subsequent five years. CA-125 evaluation in 2024 confirmed sustained complete remission.

4. Case 3

A 39-year-old female presented in July 2014 with abdominal pain, hypertension, and oligomenorrhea. Left ovarian mass biopsy revealed a primary serous cystadenomatous tumor. PET-CT scan demonstrated a large, metabolically active solid mass replacing the left ovary. Additionally, focal thickening with increased metabolic activity in the gallbladder fundus with contiguous involvement of liver segment IVB suggested primary gallbladder adenocarcinoma. Histopathological examination revealed a left ovary measuring 8.5 x 5.5 x 3 cm with papillary projections, breached capsule, multiple peritoneal deposits, and pleural effusion. Following diagnosis, the patient received two cycles of chemotherapy before undergoing TAH with BSO. Post-operative management included six cycles of chemotherapy followed by oral metronomic chemotherapy with etoposide and tamoxifen. Regular follow-up over ten years until October 2024, including CA-125 monitoring, confirmed complete remission while maintaining metronomic therapy.

5. Case 4

A 58-year-old female presented in December 2018 with abdominal pain. CT imaging revealed omental thickening, bilateral adnexal masses, ascites, gastroesophageal junction thickening, and retroperitoneal lymphadenopathy. Upper gastrointestinal endoscopy demonstrated gastroesophageal reflux disease with hiatus hernia. Ascitic fluid cytology confirmed adenocarcinoma, establishing the diagnosis of epithelial ovarian carcinoma. The patient commenced combination chemotherapy (bortezomib, doxorubicin and dexamethasone), receiving cycle 1 on December 25, 2018, and cycle 2 on January 17, 2019. Following an episode of febrile neutropenia requiring antibiotic treatment on January 28, 2019, she completed three cycles of chemotherapy before undergoing TAH with BSO, bilateral pelvic lymphadenectomy, retroperitoneal lymphadenectomy, and omentectomy. Post-operative imaging revealed left external iliac and femoral vein thrombosis with retroperitoneal and mesenteric lymphadenopathy after completing six cycles of chemotherapy. In June 2019, she was initiated on oral metronomic chemotherapy with etoposide and tamoxifen. Follow-up investigations, including blood work and

abdominal ultrasound, showed normal results after two months. In 2024, despite presenting with abdominal pain, PET-CT scan confirmed complete disease remission, leading to the discontinuation of metronomic therapy.

6. Discussion

This case series presents four women, aged 39-65 years, diagnosed with advanced ovarian cancer between 2013-2018, who achieved complete remission following metronomic chemotherapy with etoposide and tamoxifen. All patients initially presented with abdominal symptoms and were found to have significant disease burden on imaging. Three patients received conventional chemotherapy followed by surgery and metronomic therapy, while one patient underwent metronomic therapy before and after surgery. Remarkably, all four cases demonstrated sustained complete remission during long-term follow-up, ranging from 5-10 years, as confirmed by serial CA-125 measurements and imaging studies. The successful outcomes in these cases, particularly in patients with advanced disease and complex presentations including concurrent gallbladder involvement (Case 3) and venous thrombosis (Case 4), suggest the potential efficacy of metronomic chemotherapy as a viable treatment strategy in advanced ovarian cancer.

Long-term survival in ovarian cancer is rare with conventional chemotherapy, with reports indicating a survival rate of only 18%, typically among younger patients.[10] Interestingly, in our observations, all four patients who received metronomic chemotherapy survived beyond 10 years, despite being in the middle-aged to older adult category. In one of our cases, metronomic tamoxifen and etoposide were employed as part of neoadjuvant chemotherapy, resulting in complete remission. This outcome is notable, as a prior study reported that optimal responses to neoadjuvant chemotherapy were achieved in only 51% of patients deemed unsuitable for surgical resection.[11]

Tamoxifen, widely known for its efficacy in hormone receptor-positive breast cancer, has also shown anti-tumor activity in a range of malignancies, including ovarian cancer. Incorporating tamoxifen into a metronomic regimen may leverage its diverse mechanisms of action, potentially benefiting patients with varying tumor biology. Similarly, etoposide, a long-established chemotherapeutic agent, may act synergistically with tamoxifen, highlighting a combination that merits further exploration.[12] Beyond efficacy, our series underscores the improved safety profile of this combination compared to traditional chemotherapy regimens.[13] For ovarian cancer, while individual studies have not conclusively established a survival benefit of maintenance chemotherapy, a meta-analysis indicates that continuing chemotherapy following primary treatment enhances both progression-free survival and overall survival.[12] When continuing chemotherapy after achieving complete remission, it is generally preferable to administer chemotherapeutic agents at the lowest effective doses, considering the dose-response relationship. This approach aligns with the principles of metronomic therapy, which emphasizes the use of lower, more frequent doses to minimize toxicity while maintaining therapeutic efficacy.

This case series offers several notable strengths, including the extended follow-up period of up to 10 years, which provides valuable insights into the long-term efficacy and safety of metronomic chemotherapy in ovarian cancer. The diverse patient profiles, ranging from pre-menopausal to post-menopausal women with varying disease complexities, demonstrate the potential broad applicability of this approach. However, several limitations must be acknowledged. As a small case series, the findings cannot be generalized to the broader population, and the absence of a control group prevents direct comparison with conventional treatment protocols. Additionally, the retrospective nature of the analysis limits our ability to systematically evaluate quality-of-life metrics and detailed toxicity profiles. Moving forward, these promising results warrant larger, prospective randomized controlled trials to validate the efficacy of metronomic chemotherapy in ovarian cancer. Future studies should focus on identifying optimal patient selection criteria, establishing standardized dosing protocols, and investigating potential biomarkers that might predict treatment response. Furthermore, comparative studies examining cost-effectiveness, quality of life outcomes, and the role of metronomic therapy in different disease stages would be valuable additions to the current literature. The integration of molecular profiling and immunological monitoring could also provide deeper insights into the mechanisms underlying the observed therapeutic benefits.

7. Conclusion

This case series demonstrates the potential efficacy of metronomic chemotherapy using etoposide and tamoxifen in achieving and maintaining complete remission in advanced ovarian cancer. The sustained response observed across all four cases, with follow-up periods ranging from 5 to 10 years, suggests that this approach may offer a viable therapeutic alternative to conventional chemotherapy regimens. The favorable outcomes, particularly in patients with complex presentations and advanced disease, coupled with the relatively low cost and potentially reduced toxicity profile of metronomic therapy, make this strategy especially relevant for resource-limited healthcare settings. While these results are encouraging, they should be interpreted within the context of a small case series. Nevertheless, they provide a strong rationale for larger, prospective studies to further evaluate the role of metronomic chemotherapy in ovarian cancer treatment protocols. The successful outcomes observed in these cases may represent a significant step toward developing more sustainable, patient-friendly therapeutic approaches in the management of advanced ovarian cancer.

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9. Conflict of Interest

None.

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