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# Tamoxifen use in recurrent ovarian cancer in a Chinese population: A 15 -year clinical experience in a tertiary referral center

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## Abstract

**Aim:** To review the clinical use and the effectiveness of tamoxifen in patients with advanced or recurrent ovarian cancer.

**Methods:** A retrospective review of clinical records was conducted in patients who received tamoxifen for the treatment of ovarian cancer between 2002 and 2016. We reviewed the clinical setting that it was given, duration of use, patients' tolerability, clinical benefit and progression-free survival. We also attempted to identify predictive markers for response.

**Results:** A total of 92 patients received tamoxifen during this 15-year period. The patients received a median of 2.5 lines of chemotherapy before switching to tamoxifen, and they remained on tamoxifen for a median of 5.6 months (range 0–85 months), with 24 patients receiving it for more than 12 months. Seventy-six patients continued on tamoxifen for more than 2 months. In this group, 75 patients had an evaluable response, either by CA 125 or clinically and clinical benefit rate (defined as complete, partial response and static disease) was seen in 42 patients (56%), with majority of patients having static disease. The median progression-free survival was 5.3 months (95% confidence interval, 2.6–8.1). Tamoxifen was well tolerated. Hormone receptor status was not demonstrated to predict response.

**Conclusion:** Patients with advanced ovarian cancer who have failed previous lines of chemotherapy may achieve static disease with tamoxifen with minimal side effects. Tamoxifen may still have a role in the era of molecular target therapy.

KEYWORDS
ovarian cancer, SERMS, tamoxifen

## 1 | INTRODUCTION

Ovarian cancer is the 8th most common female cancer worldwide.[1] In developed countries, it is about 10th most common but has fifth mortality among women cancers. Primary treatment is surgery, followed by platinum-based chemotherapy. However, the majority of women relapse.[2] Platinum-sensitive patients would be "re-challenged" with platinum-based chemotherapy, and the response rate can be up

to about 60%. About 20% of patients are platinum-resistant, and some who are platinum-sensitive initially will subsequently develop platinum resistance.[3–5] For these patients, non-platinum-based chemotherapy such as topotecan or liposomal doxorubicin would give a response rate of about 10–30%.[6,7] The treatment is mainly palliative with the aim of maintaining a good quality of life, but these chemotherapy agents all have significant toxicities.

In recent years, targeted therapy has emerged, such as anti-angiogenesis agents, which may prolong progression-free survival (PFS) when used in combination with chemotherapy.[8] However, these still require intravenous administration and have their specific toxicities. Oral agents such as PARP inhibitors are now available, and these have the advantage of being oral agents, but they also may have significant toxicity, for example myelosuppression.[9] More importantly, these agents are all extremely expensive and would not be affordable by the general population without substantial subsidy from the government or charity.

Ovarian cancer is classified as hormonal dependent cancer. Tamoxifen, a selective estrogen receptor (ER) modulator has long been shown to have an effect on ovarian cancer, with a response rate of about 15%, and it is generally well tolerated with minimum toxicity.[10] Tamoxifen exerts its effect by blocking estrogen signaling by binding to ERs, leading to inhibition of various molecular mechanism such as inhibition of tumor production of endothelial growth factor and reduction in tumor – endothelial cell migration via the MAPK signaling pathway.[11,12] Due to its modest response rate and the arrival of new therapeutic options, the use of tamoxifen may have become less favored. However, a recent meta-analysis demonstrated a 41% clinical benefit rate (CBR, defined as complete response, partial response and static disease) with endocrine therapy[13] and a recent phase 3 trial comparing chemotherapy to tamoxifen in women with platinum-resistant tumor showed better quality of life in the group on tamoxifen.[14] Therefore, tamoxifen may still have a role in the management of ovarian cancer patients. In this study, we aim to review the clinical use and efficacy of tamoxifen in a tertiary referral center for ovarian cancer.

## 2 | METHODS

### 2.1 | Patient characteristics

Patients with histologically confirmed ovarian, fallopian tube or peritoneal cancers who were given tamoxifen as part of their treatment were included in this retrospective analysis. Patients diagnosed with ovarian cancer in our unit would undergo primary surgery including total hysterectomy, bilateral salpingo-oophorectomy, omentectomy and pelvic and para-aortic lymphadenectomy for early disease or maximal debulking surgery for late-stage disease. Postoperatively, six cycles of adjuvant chemotherapy (carboplatin and paclitaxel) would be given. Patients would be monitored for recurrence with regular physical examination and tumor marker (CA 125). Imaging would be arranged if recurrence was suspected. Chemotherapy would be the main treatment for recurrence. Platinum sensitive patients would be re-challenged with platinum-based chemotherapy while those resistant to platinum would receive second-line chemotherapy, mainly gemcitabine, topotecan or liposomal doxorubicin. Tamoxifen would be offered to patients who had failed multiple lines of chemotherapy or those who preferred to use tamoxifen instead of chemotherapy for personal reasons such as quality of life considerations. Patients would be followed up at our clinics regularly, between 1 and 3 months, to assess toxicity and response. Since the majority of these patients were treated with palliative intent, monitoring of disease would be less intensive and more variable. The response was usually assessed clinically and by measurement of CA 125 with reference to the GCIG criteria and in some patients, radiologically using the RECIST criteria.[15,16] The clinical parameters, including patients' demographics, toxicity experienced and response to treatment, were obtained from the patients' clinical records. The ER and progesterone receptor (PR) status were obtained from the clinical pathology report. ER and PR expression were assessed by immunohistochemistry. Scoring was done according to the guidelines from American Society of Clinical Oncology/College of American Pathologists. Positivity for ER/PR was defined as ≥1% of tumor cell nuclei being immunoreactive and ER/PR was negative if finding of <1% tumor cell were immunoreactive in the presence of internal positive control.

### 2.2 | Statistical analysis

The analysis was done by IBM SPSS Statistics (Version 25). Categorical data were described by median, minimum and maximum, percentage or crosstab when it is applicable and analyzed using chi-square test. Continuous data were described in mean and standard deviation and analyzed by *t* test. The survival data were analyzed by Kaplan–Meier and log-rank test.

## 3 | RESULTS

During a 15-year period between 2002 and 2016, a total of 92 patients received tamoxifen for treatment of ovarian cancer. Patients' demographics were shown in Table 1. The median age was 55 years. 73% of patients had late-stage disease (stage III–IV) at initial diagnosis. The commonest histology was serous adenocarcinoma (60%). Majority of them received tamoxifen for progressive disease from the previous line of chemotherapy or suspected recurrence. The indications for tamoxifen were given in Table 2. The patients received a median of 2.5 lines of chemotherapy before switching to tamoxifen, and they remained on tamoxifen for a median of 5.6 months (range 0–85 months), with 24 patients receiving it for more than 12 months. However, 16 patients (17%) stopped tamoxifen within 2 months, mainly due to progressive disease. Amongst those who had continued for more than 2 months, the median duration of use was 7.7 months.

**TABLE 1** Patients' demographics

| Demographics | *N* = 92 |
|---|---|
| Age (median, range) | 55 (29–83) |
| Initial stage of disease (number,%) | |
| Stage 1 | 10 (11%) |
| Stage 2 | 5 (5%) |
| Stage 3 | 50 (54%) |
| Stage 4 | 17 (19%) |
| Unstaged/ unknown | 10 (11%) |
| Histology (number,%) | |
| Serous | 55 (60%) |
| Endometroid | 8 (9%) |
| Clear cell | 9 (10%) |
| Mucinous | 0 |
| Mixed | 6 (7%) |
| [a] Others | 14 (15%) |
| No. of previous lines of chemotherapy (number, %) | |
| No previous chemotherapy | 4 (4%) |
| One line | 18 (20%) |
| Two lines | 24 (26%) |
| Three lines | 18 (20%) |
| Four lines | 13 (14%) |
| More than four lines | 15 (16%) |
| Duration of use (number, %) | |
| <2 months | 16 (17%) |
| 2–6 months | 32 (35%) |
| 6–12 months | 20 (22%) |
| More than 12 months | 24 (26%) |

[a] Others included eight poorly differentiated adenocarcinoma, five cytology from ascitic fluid showing carcinoma cells suggestive of female genital tract origin and one carcinosarcoma.

**TABLE 2** Indication for starting tamoxifen

| Indication/reason for starting tamoxifen | Number of patients (*n*, %) |
|---|---|
| Declined first-line chemotherapy | 3 (3%) |
| Partial response or static disease from previous line of chemotherapy | 24 (26%) |
| Progressive disease from previous line of chemotherapy | 55 (60%) |
| Unfit for or refused further chemotherapy | 9 (10%) |
| Low-grade serous histology | 1 (1%) |

### 3.1 | Responses to tamoxifen

We have confined our response analysis to the 76 women who had taken tamoxifen for more than 2 months since it might not be valid to assess response with a shorter duration of use. Nine women had response monitored by imaging, but none were evaluable by RECIST criteria due to different imaging modalities used for each assessment (e.g. MRI then PET-CT, etc.). Sixty-nine women had CA 125 monitoring, of which 33 women could be assessed according to the GCIC criteria. The rest could not be assessed according to GCIC because CA 125 were not checked according to the stated time frame. Among these 33 women, 2 (6%) had complete response, 3 (9%) had partial response, 18 (55%) had static disease and 10 (30 %) had progressive disease. The CBR was 70%. One patient's response could not be evaluated due to inadequate documentation in the medical records. For the remaining patients ($n = 42$), the response was assessed clinically, based on clinical findings and tumor markers. Complete response was seen in 2 patients, 17 had static disease and 23 had progressive disease. Overall, among the 75 women who had taken tamoxifen for more than 2 months with an evaluable response, either by CA 125 or clinically, clinical benefit was seen in 42 patients (56%). The overall median progression-free survival (PFS) for the whole group ($n = 92$) was 4.1 months ((95% confidence interval [CI], 2.3–6.0). The median PFS for those who received two or fewer lines of prior chemo was 5.3 months compared to 2.6 months in those who received more than two lines of chemotherapy. In the subgroup of patients receiving tamoxifen for more than 2 months ($n = 76$), the median PFS was 5.3 months (95% CI, 2.6–8.1). The median PFS for those who received two or fewer lines of prior chemo was 8 months compared to 4.1 months in those who received more than two lines of chemotherapy.

### 3.2 | Predictive markers of response

Among 92 patients, ER status was measured in 26 patients, of which 20 were ER positive, and 6 were negative. Progesterone receptor status was measured in 21 patients, of which four were PR positive, and 17 were negative. Among 76 patients taken tamoxifen for more than 2 months, ER status was measured in 17 patients, of which 13 were ER positive, and 4 were negative. PR status was measure in 15 patients, of which two were PR positive, and 13 were negative. There was no correlation between the response rate and the ER or PR status ($P = 0.225$ and 0.245). The response among the different histological subtypes was analyzed, and there was no correlation.

## 4 | DISCUSSION

This study shows an overall CBR of 56% in women receiving tamoxifen. Although the complete and partial response rate was just below 10%, 46% ($n = 35$) of women had static disease while on tamoxifen. This is comparable to, if not better than, the CBR reported in a recent meta-analysis on endocrine therapy in ovarian cancer between 1982 and 2015.[17] Tamoxifen showed the highest CBR of 43% based on 23 studies, whereas the CBR for aromatase inhibitors (AIs) in 10 studies was 39%. Despite the large number of studies identified, only two trials had a sample size of >100 subjects, and all were retrospective or phase 2 studies. Since the publication of this review, a phase 3 randomized trial comparing tamoxifen with chemotherapy in platinum-resistant

ovarian cancer was published.[14] The primary endpoint of this study was health-related quality of life (QOL), and the secondary endpoint was PFS and OS by RECIST criteria. This study found that the patients on the chemotherapy arm had worse QOL but a longer median PFS of 12. 7 weeks versus 8.3 weeks for those on tamoxifen. Compared to the PFS reported in this phase 3 trial, our current series of 92 patients showed a slightly better median PFS of 18 weeks. For those who had received more than two lines of previous chemotherapy, which would be a more similar population to those included in the phase 3 trial, the median PFS was 11.6 weeks (2.6 months) and 18 weeks (4.1 months) for the whole population ($n = 92$) and those taking tamoxifen for more than 2 months ($n = 76$) respectively in our study. This was also comparable to the PFS in the chemotherapy arm in the phase 3 trial as well as in other large phase 3 trials on patients with recurrent ovarian cancer using targeted therapy, for example in the AURELIA trial, the median PFS in the chemotherapy arm alone was 3.4 months.[18] The PFS for those taking tamoxifen for more than 2 months in our study was longer than the PFS for the whole population, mainly due to the rapid clinical deterioration in the group who took tamoxifen for less than 2 months, many of whom was started on tamoxifen because they would be unfit for further chemotherapy.

It is difficult to directly compare our results with the published series due to the heterogeneity in the study population and the criteria for response measurement. One of the major weakness in this study is its retrospective nature with its inherent problems. We did not have a standardized protocol to assess response. This reflected the real-life clinical situation and the patients involved. About 50% of our patients had received three or more lines of chemotherapy and treatment was palliative in intent. Monitoring for responses was less intense, mainly to avoid unnecessary psychological burden for the patients and partly to reduce the financial burden on the health system. Therefore, advanced imaging was infrequently used and hence, majority of the patients could not be assessed by RECIST criteria, making it difficult for us to compare our results with those in large-scale randomised controlled trial (RCT). Nonetheless, most of our patients had CA 125 monitoring, but the frequency of monitoring was variable, thus precluding a proportion of our patients being evaluable by GCIG criteria. The retrospective nature of our study also precluded a detailed assessment of side effects as there was likely to be inconsistent recording of toxicity outside a prospective clinical trial. Nonetheless, only one patient stopped tamoxifen due to side effect (breast pain), suggesting that tamoxifen was generally well tolerated.

Growth inhibitory effects of anti-estrogen were strongly related to ER expression in vitro, and it was anticipated that this would translate to a higher clinical response rate in women with ER expressing tumors.[19,20] However, the role of ER status and response to tamoxifen had been debatable. Tamoxifen was thought to act via ER, but there were at least 2 ER subtypes – ER alpha and ER beta, which were shown to have opposite activity with ligand binding in preclinical studies.[21] There was also the cytoplasmic pathway in addition to the classic nuclear pathways for ER to exert its actions. All these may add to the complexity of tamoxifen's mechanism of action and clinical effect. In a recent meta-analysis, subgroup analysis by hormone receptor status showed no significant difference in response in relation to receptor status and our result was also consistent with this finding. Meanwhile, in a GOG trial of tamoxifen, eight out of nine complete responders had elevated ER expression.[22] In the majority of the studies reported (and ours included), ER status was only available in a small proportion of subjects and heterogeneity in ER expression in the same tumor or between the primary tumor and metastases might have led to the inconclusive results. In a collaborative Ovarian Tumor Tissue Analysis consortium study involving tissue microarrays from 2933 women with epithelial ovarian cancer, ER expression was associated with improved survival in the endometrioid subtype only.[23] In our current study, we did not find any correlation between histological subtypes and response to tamoxifen, possibly due to the small proportion of women who had ER status ascertained.

The high proportion of women achieving static disease and the good general tolerability is encouraging, bearing in mind the aim of treatment in this group of women is disease control while maintaining a good quality of life. Nonetheless, our study cannot determine whether the outcome was an effect of tamoxifen or from the natural biology of the disease. A placebo controlled RCT would be needed to answer this question. Our study suggests that there may still be a role for hormonal therapy in the era of molecular targeted therapy. Other hormonal therapy, such as AI or selective ER degrader (SERD) had also been studied. Early phase 2 studies on fulvestrant (SERD) and letrozole (AI) showed a clinical benefit of 43% and 51% respectively,[24,25] and a more recent retrospective analysis showed no significant difference in CBR between AI and tamoxifen. With similar CBR, tamoxifen may be the most attractive option due to the oral administration (compared to Fulvestrant, which requires injections), good side effects profile compared to AI and the overall low cost. In the era of personalized molecular treatment for ovarian cancer, receptor subtype-selective treatment and combination of new molecular targets such as mTOR inhibitors, CDK4/6 inhibitors and MEK inhibitors would need to be further explored.

## CONFLICTS OF INTEREST

The author declares no conflicts of interest.

## ETHICS APPROVAL STATEMENT

This study was approved by the institution's ethics review board (UW 20-094).

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