Hormonal treatment of advanced serous borderline ovarian tumours: four patients with response to hormonal therapy

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Abstract
Treatment of advanced or recurrent borderline ovarian tumours is mainly surgery-based while the results of chemotherapy are unsatisfactory. The majority of borderline ovarian tumours express oestrogen receptors and few cases of response to various hormonal treatments have been reported. We describe four cases of recurrent borderline ovarian tumours expressing oestrogen receptors that were successfully treated with tamoxifen 20 mg/daily. In no case did we observe a complete remission of the disease, but in all cases a clinical and serological response was observed. In one patient, disease control was maintained for several years. In one case, after progression during tamoxifen treatment, a response was achieved with a doubling of the tamoxifen dose. Two out of 4 patients are alive on tamoxifen treatment and in remission from 10 and 15 months, respectively. In conclusion, these data support the hypothesis that hormonal treatment represents a useful option for recurrent borderline ovarian tumours.

Key words: borderline ovarian tumours, tamoxifen

Introduction

Borderline ovarian tumours (BOTs), also referred to as tumours of low malignant potential [1], represent a specific category of ovarian surface epithelial-stromal neoplasms that are characterized histologically by epithelial proliferation, but a principal diagnostic criterion for diagnosis is the absence of obvious stromal invasion [2]. BOTs comprise 15–20% of all ovarian malignancies and are characterized by an earlier stage at presentation, longer survival and late recurrences [3-5].

According to the FIGO staging system, 68% are Stage I, 11% Stage II, 21% Stage III and <1% Stage IV. Peritoneal implants on serosal and omental surfaces are found in 20–46% of patients [6] and, where invasive, they are associated with poor prognosis [7, 8]; para-aortic and pelvic lymph node involvement is found in 7–23% of cases with node sampling at the time surgery; while few patients develop postoperative distant disease in cervical scalene lymph node [9-11].

Complete surgical staging is of great importance. Patients with early stage tumours are usually treated by surgery alone with long-term follow-up to detect late recurrences. Adjuvant chemotherapy is often reserved for those patients with invasive implants, bulky unresectable residual tumour or clinically progressive disease [2]. Some patients, in particular patients with advanced-stage serous borderline ovarian tumours (SBOTs), develop recurrent neoplasms and a small percentage of them eventually die of their disease, despite an extended survival [4, 8]. Although there are some reports describing complete response to platinum-based chemotherapy in patients with advanced-stage SBOTs with microscopic residual disease [12-14], the value of medical therapy in patients with BOTs remains controversial [7].

Epidemiological studies have indicated a relationship between ovarian cancer and gonadal steroid hormones: expression for oestrogen receptor α, oestrogen receptor β, and progesterone receptor has been demonstrated in epithelial cells of normal ovaries, in benign, borderline and malignant ovarian tumours [15].

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CANCER BREAKING NEWS 2013;1(1):18-21

Oestrogens have been shown to stimulate cell proliferation in cells containing oestrogen receptor (ER), and use of oestrogen replacement therapy has been suggested to cause an increased risk for ovarian cancer in several studies [16-19], while progesterone has been proposed to exert a protective role against ovarian cancer. Anti-oestrogen therapy with tamoxifen has induced tumour shrinkage in some patients with platinum-refractory recurrent ovarian cancer [20].

The role of hormonal treatment of advanced or recurrent BOTs has been poorly studied. Only few cases of recurrent BOTs treated with hormonal treatment have been reported in the literature [21, 22].

We present four cases seen at our clinic of patients with recurrent serous BOT, ER+, who received hormone therapy based on tamoxifen.

Patients

Case report 1

In January 2001, F.B., a 70-year-old woman, went on an explorative laparoscopy for an advanced-stage III ovarian tumour and was judged inoperable. Successively, she received six cycles of carboplatin plus paclitaxel with slight CA 125 level reduction and stable disease on CT scan. A laparotomy showed stable disease and radical surgery was not possible. On histology, a serous papillary BOT was diagnosed.

From August 2001 to May 2005 the patient received hormone therapy with tamoxifen 20 mg daily; this induced a >50% reduction in CA 125 level that remained stable for more than 3 years.

In May 2005, on the appearance of ascites and CA 125 increase, the patient received three cycles of carboplatin and caelyx. Chemotherapy was not effective and the patient died due to progression in November 2005.

Case report 2

A.R., a 29-year-old woman received a diagnosis of invasive ovarian cancer stage FIGO IC in 1986 in a different institution and was treated with six cycles of adjuvant platinum-based chemotherapy. In 2003, a recurrent pelvic mass was surgically removed and, after surgery, the patient received further six cycles of paclitaxel and carboplatin. The following year, the tumour metastasized again and she was admitted to our hospital. Radical surgery was performed with a histological diagnosis of recurrent oestrogen receptor positive BOT. No adjuvant treatment was performed.

A third relapse occurred in 2010 with disease localized in the rectal anterior wall, abdominal wall, and lumboaortic lymph nodes, along with a CA 125 increase. The recurrence was only partially resected and the patient started tamoxifen 20 mg/daily in October 2010. At the last follow-up visit in April 2012, the CA 125 level had returned to normal, with a 25% reduction in the major diameter of the pelvic mass. Progression occurred in December 2012. A double dose of tamoxifen was prescribed but further progression occurred in June 2013. Chemotherapy is now ongoing.

Case report 3

In 2001, F.M.C., a 55-year-old woman, received a diagnosis of stage IC ovarian cancer in a different institution and was treated with six cycles of platinum-anthracycline-based chemotherapy. In January 2008, she underwent laparotomy due to increased CA 125 and a relapse with microscopic peritoneal implants was observed. This was followed by six cycles of paclitaxel and carboplatin chemotherapy with stable disease after 3 and 6 cycles. In November 2008, due to progression of ascites and an increase in CA 125, she was admitted to our hospital and received liposomal doxorubicin with stable disease after 3 cycles.

In February 2009, a review of the histological examination of the previous surgery revealed a serous oestrogen receptor positive BOT. Thus, chemotherapy was stopped and the patient was treated with tamoxifen 20 mg/day. Seven months of tamoxifen treatment resulted in a reduction in CA 125 levels and ascites. In October 2009, due to an increase in CA 125 levels and ascites requiring paracentesis, the tamoxifen dose was increased to 40 mg/daily. Again CA 125 levels were reduced and no paracentesis has been required for about 10 months. The patient progressed in August 2010 and was treated with platinum-based chemotherapy.

Case report 4

In 2003, V.C., a 52-year-old woman, received a diagnosis of stage IC ovarian cancer in a different institution, underwent surgery and was treated with 6 cycles of platinum-taxane-based chemotherapy. On recurrence the patient underwent surgery in 2004 and was treated again with platinum-based chemotherapy, and underwent surgery again in 2005 without receiving any adjuvant chemotherapy. Another abdominal recurrence occurred in 2007 when the patient was admitted to our hospital. Surgery was radical with cytoreduction of peritoneal nodules. Histology revealed again a serous progesterone receptor positive, oestrogen receptor negative BOT. Thus, the patient was treated with megestrole acetate and the therapy was continued for 3 years. No further recurrence has been recorded.

Discussion

Unlike women with invasive carcinoma, those with BOT tend to present at an earlier stage, and patients with stage I and II BOT have a risk of recurrence of 12.1% and 26%, respectively [23].

There is no consensus regarding treatment of recurrent or advanced borderline ovarian tumours. BOT tend to be resistant to chemotherapy or radiotherapy [10, 24] and, when possible, surgery remains the only effective option [25]. Patients with unresectable disease are usually treated with chemotherapy [2]; however, only a few cases responding to chemotherapy have been described in the literature and, usually, the results of antiblastic therapy are considered unsatisfactory [7].

Tamoxifen is frequently used in recurrent ovarian cancer refractory to chemotherapy and a response rate of up to 11% has been reported, although studies were performed in small series of patients [15, 22, 26].

Several authors have reported that a significant expression of oestrogen receptors and progesterone receptors is a frequent finding in BOT [15, 26]. In one report, 94% and 100% of serous and mucinous borderline tumours were oestrogen receptor positive with 76% of oestrogen receptor positive cases with >25% of immunoreactive tumour nuclei [26]. Accordingly, a few cases of BOT treated with hormonal agents have been reported in the literature [15, 21, 22, 26]. Two were cases of recurrent chemotherapy-resistant serous BOT, in which tamoxifen induced a complete remission [22, 26]. Another case was an advanced serous BOT suboptimally debulked that was treated with leuprolide that induced a complete clinical and serological response [27]. Furthermore, Lee et al. [21] have described a case of a serous BOT metastatical to the sigmoid colon, successfully treated with the aromatase inhibitor anastrozole inducing a complete remission of the disease.

Conclusion

In the present study, we report three cases of recurrent serous BOT treated with tamoxifen and one treated with megestrol acetate. All of these cases had been previously treated with chemotherapy with unsatisfactory results (no response; stable disease in two cases). In all cases, the diagnosis was obtained later during the clinical history because of a previous erroneous diagnosis of invasive carcinoma, thus confirming the importance of dedicated ovarian cancer centres for accurate pathological assessment. In our experience (unpublished data), when the histology was reviewed in our institution, there was frequent discordance among the pathologists regarding the invasivity of peritoneal implants. In three out of four cases, oestrogen receptor expression was positive, while one case was progesterone receptor positive and oestrogen receptor negative, confirming that the majority of serous BOT express hormone receptors. In the three patients treated with tamoxifen, long-lasting control of the disease lasting several months was obtained. In two cases, after progression a doubling of the tamoxifen dose induced a recovery of the response, suggesting a possible dose-related effect. In the progesterone receptor positive/oestrogen receptor negative case, with several abdominal recurrences treated with surgery, long-term remission has been achieved with progestins.

These data seem to confirm that hormonal treatment is a valid option for the treatment of advanced or recurrent serous BOT. It is a nontoxic treatment that has been shown to be safe in other cancers when given over a long period of time. In this setting, it compares very favourably with chemotherapy, which induces questionable response rates and more toxic effects.

In conclusion, hormonal therapy proved to be effective in four cases of recurrent serous BOT confirming that hormonal treatment represents a very attractive option for these patients.

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