CASE REPORT

Aromatase inhibition in relapsing low malignant potential serous tumours of the ovary

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SUMMARY

Low malignant potential serous tumours (LMPSTs) of the ovary represent an indolent disease, with an excellent prognosis in a majority of patients. Patients with recurrent LMPSTs tend to develop widespread disease with a mortality rate as high as 70%. These tumours tend to have a very poor response to standard chemotherapy, and the management of primary and recurrent disease beyond surgical resection is not well defined. The majority of LMPST have been reported to express oestrogen and progesterone hormone receptors. However, only three reported cases of antihormonal treatment in this setting, and only one using aromatase inhibitors (AI), have been previously reported. We herein report long-term complete remission of two patients with relapsed, chemotherapy-resistant LMPSTs, treated with long-term AI (anastrozole 1 mg daily) as per negative MRI and positron emission tomography scans. Our results warrant further investigation for the use of AIs for metastatic recurrent LMPSTs.

BACKGROUND

Low malignant potential serous tumours (LMPSTs) of the ovary, also called borderline tumours, are a heterogeneous group of lesions defined histologically by atypical epithelial proliferation without stromal invasion.¹ They comprise about 15–20% of all epithelial ovarian malignancies with an incidence of 1.8–4.8 cases per 100 000 women per year.² The prognosis of LMPSTs is generally excellent; however, 11% of these tumours recur and 20–30% of relapses exhibit malignant transformation.³ The pathological stage of disease and subclassification of extraovarian disease into invasive and non-invasive implants, together with the presence of postoperative macroscopic residual disease, currently appear to be the major predictors for recurrence and also for survival.⁴ Eventually, up to 70% of the patients who have a recurrence of LMPSTs will die of their disease.⁵ The primary modality of treatment for LMPSTs and recurrent tumours is surgical resection. The role of chemotherapy in LMPSTs, even in advanced stages, remains controversial with mixed outcomes published in the literature.³

Given the rarity of these diseases, the optimal management beyond surgical resection of patients with relapsed LMPSTs remains to be elucidated. Hormone receptor status has been reported to be positive in between 49% and 94% of the LMPSTs of the serous subtype.^{6 7} However, to this date, outcomes of only three patients with LMPSTs treated with antihormonal therapy, only one of

which received aromatase inhibitors, have been reported.^{8–10} Here we report our experience using anastrozole in patients with relapsed chemotherapy-refractory LMPSTs.

CASE PRESENTATION

Case 1

In 1985, a 34-year-old woman with no remarkable medical history presented with a 2-week history of increasing abdominal girth and abdominal pain, and was found to have ascites and a pelvic mass on examination. She underwent laparotomy for the resection of a pelvic tumour adherent to the uterus and ovaries. A total hysterectomy, bilateral salpingo-oophorectomy (TAHBSO) and omentectomy was performed with negative ovarian tumour margins. She was subsequently initiated on hormone replacement therapy.

The histological examination revealed an LMPST with the expression of a micropapillary pattern involving both ovaries and fallopian tubes, the myometrium, the pelvic cavity and the omentum. The patient received adjuvant chemotherapy with one cycle of CAP (cyclophosphamide, doxorubicin, cisplatin) that was complicated by excess gastrointestinal toxicity, and was subsequently switched to cyclophosphamide and carboplatin for four cycles. There was no residual disease on a CT scan postchemotherapy. In 1991, a right hydronephrosis was documented and a surgical resection confirmed a small recurrence in the area of the right ureter. No further treatment was given after surgery given the absence of other foci of disease.

In 1992, malignant infiltration of the spleen was seen on a CT scan, and the patient underwent a splenectomy. The pathology showed a 5.5 cm nodule, surrounded by multiple intrasplenic foci of metastatic papillary LMPSTs, consistent with recurrence of the initial tumour. The immunohistochemistry (IHC) performed was positive for estrogen receptor (ER, moderately positive in the majority of tumour cells) and progesterone receptor (PR, weak-moderate expression in >10% of cells). Again, the patient did not receive further treatment at that time given her asymptomatic state.

In 1998, the patient underwent an urgent repair of a perforated bladder, with pathological examination revealing a local recurrence of her LMPST. She was then started on chemotherapy with three cycles of carboplatin and paclitaxel, with no response. Given the unsatisfactory response obtained with chemotherapy and her asymptomatic state, the patient was followed closely.

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In 1999, a nodule in the right adnexal region was visualised on CT scan and MRI, indicating progressive disease. The patient agreed to discontinue hormone replacement therapy, and she was started on tamoxifen 20 mg daily. After an initial reduction in size of the mass on physical examination, progressive disease was documented by ultrasound and MRI after 8 months of treatment; there was at that time a pelvic lesion measuring 9.5×6×7 cm with septations. Aspiration of the mass was consistent with an LMPST.

In February 2000, the patient was switched to anastrozole 1 mg daily. A slow but consistent gradual decrease in size of the pelvic mass was noted. After 16 months of treatment, a 50% decrease in the initial maximum diameter of her tumour was reported, although MRI still showed persistence of gadolinium-enhancing nodules in the rectum and mesentery, the largest measuring 2.5 cm. In January 2003, after 30 months of anastrozole treatment, the patient attained a radiological complete response by MRI.

Case 2

In 1999, a 53-year-old woman underwent an elective cholecystectomy. Intraoperatively, a mass involving the right fallopian tube and peritoneal seeding was found. A partial resection was performed, in addition to peritoneal and omental biopsies. The pathology report described multiple non-invasive implants of LMPSTs in the omentum, the serosa of the gallbladder, and a primary intraluminal LMPST in the fallopian tube. IHC scored a strong and diffuse staining for ER, with only very occasional staining for PR.

The patient received six cycles of adjuvant chemotherapy with carboplatin and paclitaxel from 1999 to 2000. A scan of the abdomen postcompletion of chemotherapy did not show any residual disease. The patient was subsequently treated with tamoxifen until 2004, which was discontinued when she underwent a percutaneous coronary angioplasty for acute coronary syndrome. In February 2005, the patient presented with a 2-month history of recurrent abdominal pain. A positron emission tomography (PET) scan demonstrated diffuse intense uptake in the small and large bowel, consistent with peritoneal carcinomatosis. At that time, the patient was started on anastrozole 1 mg daily for progression of her disease. A complete radiological response was documented on follow-up PET scans: within 9 months of starting anastrozole, fluorodeoxyglucose (FDG) uptake had decreased to physiological levels within the small and large bowels, and 17 months after the initiation of treatment there was no longer any FDG uptake demonstrated on her PET scan.

OUTCOME AND FOLLOW-UP

Case 1: As of January 2014, the patient remains on anastrozole without toxicity or evidence of radiological recurrence. The patient has now been in complete remission for over 11 years.

Case 2: As of September 2013, the patient was still on anastrozole without any major side effects or radiological evidence of recurrence. The patient has now been in complete remission for over 7 years.

DISCUSSION

LMPSTs have an excellent overall survival rate (FIGO stage I: 95%, FIGO stages II–IV: 70–85%), with a recurrence rate of 11% and an absolute risk of malignant transformation in 2–4%, accounting for 33% of all recurrences.³ Good prognostic factors include low FIGO stage, and the absence of postoperative macroscopic residual disease. The presence of micropapillary

pattern has been shown to be associated with a more aggressive course of disease and a higher rate of invasive peritoneal implants at diagnosis, without any impact on recurrence rates.¹¹

The role of adjuvant chemotherapy in the setting of LMPSTs is still controversial. Some studies suggest a benefit for adjuvant chemotherapy following optimal debulking surgery.^{12–14} However, the majority of studies do not show a benefit for any of the subtypes of LMPSTs.^{15–17} The poor response of LMPSTs to standard cytotoxic therapy can be attributed to their slow proliferation rate, in the adjuvant and metastatic setting. In one review, only 15.1% (8/53 patients) and 11.3% (6/53 patients) of patients had a complete or partial response, respectively, to chemotherapy for recurrent tumours.¹⁸ Given the favourable outcome of most LMPSTs, and lack of clearly demonstrated survival benefit for adjuvant chemotherapy, most physicians recommend chemotherapy after aggressive surgical debulking only if invasive implants are identified.¹⁹

LMPSTs have been reported to express hormone receptors in 49–94% of cases depending on the study and the subtype of the

Patient's perspective

When I returned home after my first surgery, I learned to appreciate fat: I was literally sitting on my bones. When I suffered the toxicity from my first chemotherapy treatment and spent four additional weeks in the hospital, I thought that I would forever see the outside world only through a hospital window.

When that magic number of '5 years' arrived, I felt that a celebration was in order, but this was not to be: one kidney had shut down and the race was to save the remaining functional one, albeit that it, too, was already somewhat compromised. Another surgery. This was devastating. My reaction was worse than when I had first been diagnosed: the first evidence that this disease was still raging in me. And, when the spleen was affected, so soon after, I was in shock. How could it be that one can feel so well and yet one is so ill? I kept saying: 'this is becoming a habit!' I felt like I was on a treadmill and could not get off. And, on it continued, with another surgery and complications at every turn, but, I was not ready to give up. I sought consultations from a number of sources, with recommendations ranging from pelvic exenteration, which I rejected, to 'no surgery' because of the already extensive adhesions I had, accompanied by repeated bowel obstructions. I was being reassured that I was receiving the best care possible in my home town.

The cancer did not succumb. And the tumour was already causing significant pain. The future looked very bleak: chemotherapy, radiation and surgery were all ruled out. No one had anything new to offer. Was I entering a palliative phase? I was not ready!

That is when my physician suggested a trial of anastrozole. In the absence of clinical trials to support the treatment of low malignant potential serous tumours with anastrozole, this was a kind of an educated leap of faith. A calculated risk. So far, I have been lucky: no side effects. I have been very lucky to have a physician who has listened at every turn, has taken seriously every report of discomfort, assisted me when I wished to consult with others and can think 'outside the box'.

I am lucky to be here today. My wish is that this report may be of value to other patients, as potentially offering physicians another weapon to add to their arsenal.

Learning points

- Low malignant potential serous tumours (LMPSTs) are indolent tumours with favourable prognosis in the majority of cases, but behave aggressively and are associated with high mortality in a subset of patients with recurrent disease.
- LMPSTs are usually resistant to standard cytotoxic chemotherapy given their slow proliferation rate.
- The majority of LMPSTs express estrogen/progesterone hormone receptors.
- Aromatase inhibitors have the potential to induce a complete long-term response, with minimal side effects, in patients with relapsed, metastatic, chemotherapy-resistant LMPSTs.

tumour.^{6,7} To date, only three case reports of response with hormone therapy in this setting have been reported. One patient was treated with tamoxifen, one with anastrozole following tamoxifen and one with leuprolide.^{7–10} Two of these patients had recurrent disease resistant to standard chemotherapy. Our two LMPST cases are similar to those published in the literature; both had recurrent diseases resistant to standard chemotherapy and both were initially treated with tamoxifen. Of interest is the fact that the response of LMPSTs to aromatase inhibitors seems to be of a much greater amplitude and duration than what has been observed with tamoxifen in our cases and in the literature.

The current cumulative evidence suggests offering hormone replacement therapy in young women undergoing TAHBSO for LMPSTs to prevent cardiovascular and osteoporotic disease, and to improve quality of life.³ However, this must be weighed against new evidence suggesting that the majority of LMPSTs of the ovary are hormone receptor positive. However, given the slow proliferative nature of these tumours, it is unlikely that the use of hormone therapy will result in rapid progression of disease. This was demonstrated in our first case where the patient was on hormone therapy for over 14 years before being switched to tamoxifen.

In conclusion, we presented two cases of LMPSTs with complete response to aromatase inhibition therapy. Our results suggest that all recurrent LMPSTs should be tested for hormone status, and in view of the long-term complete remission achieved in our patients, aromatase inhibition therapy may be the best frontline therapy for patients with metastatic disease.

Contributors LP was the treating physician for both patients and has substantially contributed to the writing and reviewing of the article. All authors have contributed to the writing and editing of the article.

Competing interests None.

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