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Case series

Norethindrone substituted for megestrol in the treatment of metastatic endometrial carcinoma: Three cases

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ABSTRACT

Megestrol is an effective palliative treatment for endometrial carcinoma. Some persons with progestin-responsive cancer continue on hormonal therapy for months or even years. In persons who respond to megestrol, long term use can cause weight gain and other side effects via activity of the drug at the corticosteroid receptor. Norethindrone is a progestin which has been used clinically for decades and which is without corticosteroid activity. We report three women with metastatic endometrial cancer responding to megestrol for whom a switch to norethindrone decreased weight gain with continued cancer control. A clinical trial of first line norethindrone for metastatic endometrial cancer could benefit people with this disease.

1. Introduction

It has long been recognized that progestin therapy can provide palliative benefit to a subset of women with advanced endometrial cancer. In their 2000 review of hormonal therapy for advanced endometrial cancer, Elit and Hirte concluded that for a population unselected by hormone receptor status, “progestin therapy provides a response rate of 10–20% and survival of less than one year in women with advanced or metastatic disease” (Elit & Hirte, 2000). Reviewed studies include one with hydroxyprogesterone, and ten others with either medroxyprogesterone or megestrol. No agent proved to be superior over the others. Subsequent phase 2 studies for this population attempted to improve on megestrol by adding tamoxifen (Fiorica et al., 2004) and subsequently tamoxifen and temsirolimus (Fleming et al., 2014). Reported outcomes for combinations were similar to those obtained with megestrol alone.

Women with hormone receptor positive endometrial carcinoma are more likely to benefit from progestin treatment. A study by Thigpen et al. compared high and low dose medroxyprogesterone and found the response rate for progesterone receptor negative tumors was 14% for low dose and 2% for high dose versus 48% and 28% for progesterone receptor positive tumors (Thigpen et al., 1999). For responding patients, progression free survival of a year or more is not uncommon. In their study of megestrol and tamoxifen, Fiorca et al. described three study participants with progression free survival of four years or more.

Although they are the only drugs that have been studied for palliative hormonal treatment of endometrial cancer, long term megestrol and medroxyprogesterone are less than ideal for this population. Patients treated for prolonged periods can suffer morbidity from the cumulative corticosteroid activity of these drugs. Both megestrol and medroxyprogesterone have activity at the glucocorticoid receptor and side effects are the same as those associated with corticosteroids (Koubovec et al., 2005; Mann et al., 1997). These include thrombophlebitis, pulmonary embolism, diabetes, osteoporosis and most importantly, weight gain. These side effects are especially problematic for persons with advanced endometrial cancer. Many persons with endometrial cancer are already obese, as this is a risk factor for developing the cancer. Persons with metastatic malignancies are already hypercoagulable.

Due to problematic weight gain in some of our patients with proven disease control on megestrol, we tried substituting norethindrone for megestrol. Norethindrone is a synthetic progestin with some androgenic and estrogen/antiestrogen activity but no affinity for the glucocorticoid receptor (Koubovec et al., 2005). Norethindrone has been used for decades as an oral contraceptive, to treat endometrial hyperplasia, and as add-back hormonal replacement for women on ovarian suppression with GHRH agonists (Chandra et al., 2016; Chwalisz et al., 2012; Schindler et al., 2008). We were not able to find reports of its use to treat advanced endometrial adenocarcinoma. Here we describe the clinical course of three patients with advanced endometrial adenocarcinoma who responded to megestrol and were then successfully switched to norethindrone.

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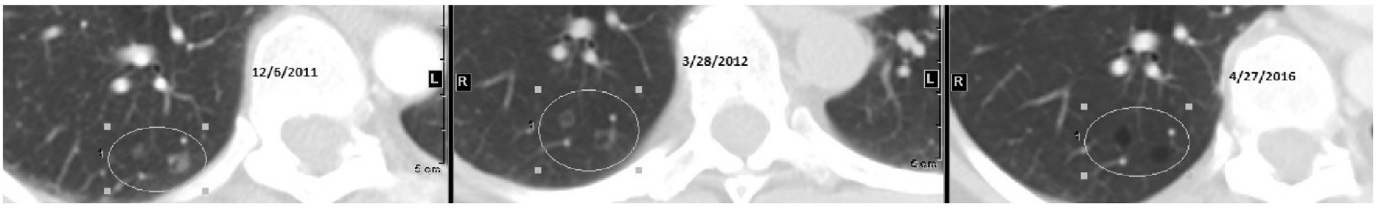

Fig. 1. Representative lung metastases are seen to first cavitate and then regress completely during endocrine therapy.

2. Case 1

A 62 year old presented with vaginal discharge and pain. She underwent hysterectomy, with pathology describing a grade 3 endometrioid adenocarcinoma with squamous differentiation. She then underwent adjuvant therapy with 6 cycles of chemotherapy, whole abdominal radiation and vaginal brachytherapy.

Surveillance imaging of the chest 19 months after completing chemotherapy commented on questionable new subcentimeter nodules. Repeat imaging was not done until 1 year later, at which time interval growth of these nodules and new nodules were noted. The largest was still only 5 mm. Thoracoscopic biopsy of a right upper lobe nodule confirmed metastatic endometrioid adenocarcinoma with squamous differentiation. Malignant cells expressed estrogen receptor.

Because of the indolent growth of these nodules together with estrogen receptor positivity it was decided to try megestrol. In January 2012 she began megestrol at 80 mg twice daily. Initial repeat imaging at 2 months showed the larger nodules to have cavitated and they subsequently slowly regressed (Fig. 1).

By February 2013 she had gained 20 kg and was struggling with lymphedema. We decided to try switching from megestrol to norethindrone 0.35 mg daily, with a plan to switch back if her disease began to progress. By April 2014 she had lost 13 kg with improved control of her lymphedema, and without progression of her lung nodules on surveillance CT imaging. Seventy-five months after starting progestin for metastatic endometrial cancer and 62 months after switching to norethindrone she has no evidence of progression and no side effects.

3. Case 2

A 62 year old nonsmoking woman was diagnosed with squamous carcinoma of the lung in 2004. This was metastatic to multiple lung sites on presentation and over the ensuing 4 years she received four courses of palliative chemotherapy. In 2008 because of her lack of symptoms and very slow progression of her lung lesions, treatment stopped and she was followed with serial imaging only.

In February 2009 she developed vaginal bleeding and was found to have a uterine mass. Pathology described a grade 2 endometrioid adenocarcinoma with extensive squamous metaplasia. Hormone receptors were not checked. In the belief that this was a second primary cancer she underwent surgery followed by internal and external radiation. In December 2011 surveillance imaging found her to have a pelvic mass which on biopsy was called metastatic adenocarcinoma and she was referred.

In January 2011 she began megestrol at 400 mg daily, with initial CT at 2 months calling slight growth in pelvic masses. She continued on megestrol and by June 2012 CT imaging showed response in the pelvis. Surprisingly she also had a marked response in the lung lesions which in retrospect must have been metastases from her endometrial carcinoma presenting 5 years before the primary tumor. In June 2013 her tumors seen on CT continued to regress but she had become wheelchair bound because of decreased strength and weight gain. She additionally developed new diabetes. She was switched to norethindrone 5 mg daily. She experienced subjective improvement and her tumor masses continued to regress.(Fig. 2) In October 2015, 48 months after starting progestin treatment and 28 months after switching to norethindrone, imaging described questionable increase in one lung mass as well as a new pelvic nodule, with stability at other sites. She was switched back to megestrol 80 twice daily. CT scan done December 2015 described stability of these lesions. Recurrent pneumonia and increasing debility precluded further imaging, and she died of complications of urinary tract infection in March 2016.

4. Case 3

A 54 year old woman presented in 2007 with uterine adenocarcinoma and underwent surgery followed by radiation. In November 2010 she developed a cough with hemoptysis and was found to have multiple lung nodules, which on biopsy proved to be metastatic adenocarcinoma

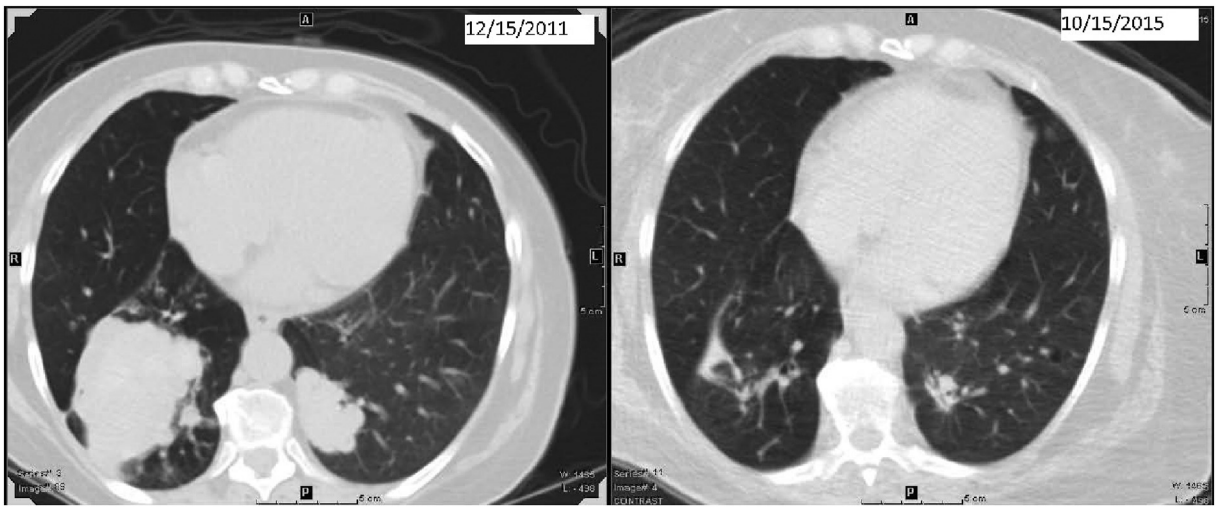

Fig. 2. Large metastatic lesions in the lung are seen to regress almost completely during megestrol followed by norethindrone therapy.

with squamous differentiation, positive for estrogen receptor. She was treated with carboplatin and paclitaxel. Her treatment was complicated by a cerebrovascular accident and hemiplegia. She completed her chemotherapy in April 2011 with an excellent response.

In November 2014 a residual abnormality on chest CT was seen to have grown from 1 to 2 cm. This was not treated, and by May 2015 this nodule had grown to 3 cm. She began megestrol at 80 mg bid and repeat imaging August 2015 showed the mass to have regressed. By February 2016 the lung nodule continued to regress, but the patient had become wheelchair bound because of her residual hemiplegia and 16 kg weight gain. She was switched to norethindrone 5 mg, but discontinuation of megestrol was complicated by acute adrenal insufficiency necessitating restart and slow taper of megestrol over one month. Adrenal insufficiency is another corticosteroid-like side effect of megestrol which has been previously described (Dev et al., 2007) On norethindrone, she lost 4 kg over the ensuing year. At the time of this writing she has been on progestin for 2 years and norethindrone for 15 months, with stability of her lung nodule and her weight.

5. Discussion

These three women with advanced endometrial adenocarcinoma responded to hormonal treatment with megestrol but suffered corticosteroid-type side effects after months on treatment. They were switched off megestrol to norethindrone, with resolution of side effects and continued disease control for many months. It is interesting that all three had endometrioid adenocarcinoma with squamous differentiation. In their phase II study, Fiorca et al. noted this histologic variant to respond to hormonal treatment (Fiorica et al., 2004). Also interesting is that after the switch to norethindrone, all three of the described women had or have a hematocrit slightly higher than normal (between 41 and 45). An elevation of hematocrit in women taking norethindrone has been previously described (Derham & Buchan, 1989). The mechanism behind this is not known but could be due to action of this drug at the androgen receptor.

This report should not be taken to mean that norethindrone is equivalent to megestrol in the treatment of metastatic endometrial cancer. All of our patients start on megestrol first as it is the standard of care for palliative treatment of endometrial cancer which might be progestin responsive, and all continue on megestrol long enough to establish response or stability of their disease. Patients are switched from megestrol to norethindrone only if they struggle with weight gain, which is not universal. The above cases describe our successful efforts to mitigate megestrol-related side effects while maintaining effective progestin treatment. We chose norethindrone because of its favorable side effect profile and its decades-long track record of safe use as a contraceptive and in the treatment of benign uterine conditions.

These case indicate a need for data supporting the use of norethindrone in the first line. Patients could avoid megestrol-related side effects altogether. Women with metastatic well-differentiated endometrial cancer would be well served by a clinical trial investigating the efficacy and side effect profile of norethindrone or another progestin without activity at the corticosteroid receptor.

Conflict of interest statement

None of the three authors on this report have any relevant conflicts of interest.

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