

Premenopozal Meme Kanseri Hastada Löprolid Asetat Etkinsizliği Sonucu Gebelik Gelişimi: Vaka Sunumu

Failure of Ovarian Ablation with Leuprolide Acetate in A Pre-Menopausal Breast Cancer Patient with Metastasis Resulting in Pregnancy:

A Case Report

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Abstract

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Ovarian ablation was the main target of systemic therapy for breast cancer. In premenopausal women, the ovaries are the predominant source of estrogen synthesis and by this reason treatment options are oophorectomy, ovarian irradiation and luteinizing hormone releasing hormone (LHRH) analogues such as goserelin acetate (GA) and leuprolide acetate (LA) which act on the hypothalamic-pituitary-ovarian axis to suppress the hormones. Rarely these agents cannot succeed and patient may become pregnant who was under treatment of LHRH analogues. We report a premenopausal patient with breast cancer in whom ovarian ablation failed while on leuprolide acetate treatment. A 34-year-old woman was presented with bone metastatic left breast cancer. Tamoxifen 10 mg twice a day, LA 3.75mg SC every 28 days and zoledronic acid 4mg IV every 28 days were started. In May 2013, receiving LA since 7 months, the patient reported a 3-4 kg weight gain and felt movement in the abdomen due to pregnancy. To date there are 4 published case reports, patients receiving GA due to breast cancer in whom a failure in ovarian ablation. All of four cases failed after at least 15 months of treatment but our case was the earliest failure of LHRH analogues in the literature and it was failure with LA, not GA as like as the other cases. It is essential for clinicians to be aware and suggest to the patients of the potential risk of pregnancy despite using the LHRH analogs.

Keywords: GnRH analogs, Pregnancy, Breast Cancer

Özet

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Over ablasyonu meme kanserinin temel hedeflerinden biridir. Premenopozal kadınlarda overler östrojen sentezinin ana kaynağıdır ve bu nedenle tedavi seçenekleri olarak ooforektomi, over radyoterapisi veya hipotalamik- pituitar-overyan aksın baskılayıcı luteinize hormone analogları (löprolid asetat, goserelin asetat gibi) bilinmektedir. Çok nadiren bu ajanlar etkili olmayarak LHRH analogları kullananlarda gebelik gözlenebilir. Biz löprolid asetat (LA) kullanırken gebe kalan meme kanserli bir vaka sunduk. Otuz dört yaşında kadın hasta kemik metastatik meme kanser tanılı tamoksifen 10 mg günde 2 kez ve 28 günde bir LA 3.75 mg cilt altı ve zoledronik asit 4 mg intravenöz uygulama ile takip edilmekteydi. Mayıs 2013'te 7 aydır LA asit kullanmakta iken hastada 3-4 kg kilo artışı, karında hareket hissi tarifledi ve gebelik tanısı konuldu. Bugüne kadar LHRH analogları ile tedavi altında iken toplam 4 gebelik vakası bildirilmiştir ancak bu vakaların hepsi GA kullanmakta idi. Tüm vakalar en az 15 aydır GA kullanmakta olup bizim vakamız en erken dönemde LHRH kullanırken gözlenen gebelik vakasıydı. Klinisyenler LHRH kullanan hastalarda gebelik açısından dikkatli olmalı ve hastaları olası riskler için bilgilendirmeliler.

Anahtar Kelimeler: GnRH analogları, Gebelik, Meme kanseri

Introduction

Ovarian ablation was the main target of systemic therapy for breast cancer and has been in use for longstanding, producing responses in approximately 30% of unselected women with metastatic breast cancer¹. In premenopausal women, the ovaries are the predominant source of estrogen synthesis and by this reason oophorectomy and ovarian irradiation have historically been used to achieve the goal of ovarian ablation. Lately, luteinizing hormone releasing hormone (LHRH) analogues such as goserelin acetate (GA) and leuprolide acetate (LA) which act on the hypothalamic-pituitary-ovarian axis to suppress circulating estrogens levels, have changed the treatment choice with permanent amenorrhea as like as older treatment choices². The effect of LHRH analogues depends on the dosage and administration. Small and repeated doses stimulate the ovary and induce ovulation but long-acting derivatives block hormonal receptors and produce an ovarian suppression in patients with breast carcinoma³. Rarely these agents cannot succeed and patient may become pregnant who was under treatment of LHRH analogues. To date there are 4 published case reports, patients receiving GA due to breast cancer in whom a failure in ovarian ablation. We report a premenopausal patient with breast cancer in whom ovarian ablation failed while on LA treatment.

Case report

In Sep 2011, a 34-year-old woman was presented with bone metastatic left breast cancer. Tru-cut biopsy confirmed a poorly differentiated infiltrating ductal carcinoma and immunostains of the tissue revealed the tumor to be estrogen receptor positive, progesterone receptor negative and Human epidermal growth factor receptor 2 (HER-2neu) negative. After the diagnosis, patient received 4 cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy and PET CT showed fully regression of the all bone metastasis. Patient had modified radical mastectomy and revealed a T3N3 pathologic examination. In addition, patient received 5 cycles of FEC regimen and then PET CT showed no pathologic uptake. Amenorrhea occurred shortly after starting the first cycle of FEC chemotherapy. After this period the patient loss of follow up so she could not receive her further therapy. On October 2012, patient had a complaint of lumber pain and also she

had regular menses with active estradiol, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) hormones since 2 months. Serum tumor markers were elevated and a PET CT scan showed multiple bone metastases and left axillary and supraclavicular multiple metastatic lymph nodes. Tamoxifen 10 mg twice a day, LA 3.75mg SC every 28 days and zoledronic acid 4mg IV every 28 days were started. Injections were administered at the oncology clinic. Amenorrhea occurred shortly after starting the first injection of LA. The patient reported hot flashes throughout her course of treatment with LA. There was no biochemical evidence of (serum estradiol, LH or FSH levels) ovarian function based on the presence of amenorrhea. In May 2013, receiving LA since 7 months, the patient reported a 3-4 kg weight gain and felt movement in the abdomen. A home pregnancy test was positive and an abdominal ultrasound revealed a singleton 21 week and 4 day old gestation with normal fetal activity and anatomy. Because of clinically progression of breast cancer, a detailed interdisciplinary discussion was done with patient and her family, and a PET CT scan followed by therapeutic abortion was planned.

Discussion

We describe a case of premenopausal patient with breast carcinoma who received leuprolide acetate at ablative doses, amenorrhea and hot flashes were present, but a gestation was detected after 3 months of treatment. This is the first case in the literature that showed the failure of leuprolide acetate. Patient with breast cancer have benefit from hormonal therapy, especially those whose tumors hormonally positive for estrogen or progesterone. The effect on the ovary depends on the drug, the dosage, and the patient's age³. A partial ovarian suppression is achieved with estrogen and progesterone derivatives. Two-thirds of patients treated with tamoxifen have normal menses⁴. Ablative methods include pelvic radiotherapy, surgery and chemical castration by LHRH analogues [3]. Emons and Schally studied the role of LHRH analogues in low-risk metastatic breast cancer with hormone receptors and reported a 50–78% response rate⁵. Amenorrhea appears in all patients and hot flashes in 84% of population with under treatment of LHRH analogues³ but rarely pregnancy should become. To date there are four case reports in the literature revealed that patients became pregnant with LHRH analogues usage in patients with cancer.

Jimenez-Gordo et al presented first 2 cases. A 36-year-old woman was diagnosed with locally advanced breast cancer. She treated with chemotherapy and surgery followed by hormonal therapy including GA (3.6 mg subcutaneous at 4-week intervals). The second case was a 41-year-old woman who was diagnosed with locally advanced breast cancer and during the follow up period she became metastatic disease and treated with subcutaneous GA, 3.6 mg every 28 days. Two patients became pregnant after 18-24 months of GA treatment. The third case reported by Vandenput et al.⁶ was a 31-year-old female who presented with a pT2N3aM0 receptor positive breast carcinoma and with a history of Hodgkin's disease. The patient was treated with a modified radical mastectomy, six cycles of systemic chemotherapy and a combination of tamoxifen and goserelin (3.6 mg SC every 28 days). After 2 years of treatment, bone metastases were found; tamoxifen was replaced with exemestane and goserelin was continued. A 14-week singleton pregnancy was discovered 14 months later⁶. The fourth case also presented in 2011 by Hill and et al⁷. A 26-year-old woman with a clinically locally advanced right breast cancer with an estrogen receptor negative, progesterone receptor weakly positive. She received six cycles of neoadjuvant chemotherapy with a rapid and complete clinical response and followed by surgery and radiation therapy. In January 2010, after 18 months of treatment with goserelin, the patient became pregnant with a positive home pregnancy test and an abdominal ultrasound. Also the last 2 case became pregnant with GA and after 18 and 24 months of the treatment. Our case was the earliest failure of LHRH analogues in the literature but it was failure with LA not GA as like as

the other cases.

Following the goserelin administration a continuous decrease in the levels of LH, FSH, and estradiol⁸. But also there are reports about the initial stimulation, followed by hormonal suppression^{5,9}. Brambilla et al. observed a continuous fall in estradiol levels, a transitory rise in progesterone levels, and variable responses in LH and FSH¹⁰. They identified two subgroups of patients: some had high initial levels of LH, and treatment reduced these levels of hormones, whereas some others had low initial levels which increased during the first week of treatment and then declined during the first month until ablation³. To date we do not know that LA or GA more effective to achieve chemical castration in patients with breast cancer. Also failure at short term or long term are the questions that waiting the answer. We can speculate that, following the administration of GnRH analogs "flare up" effects occurs during the first week. This effect may cause a temporary rise of gonadotrophins (FSH and LH). In our case this mechanism can explain the possible underlying cause of ovulation and ensuing pregnancy after the first GnRH application. But in other case reports the underlying mechanism of pregnancy cannot be speculated by this way. There may be an insensitivity to GnRH analogs after some time; receptor insensitivity! Or drug inactivity for some reasons.

Conclusion; It is essential for clinicians to be aware of and suggest to the patients of the potential risk of pregnancy despite using the LHRH analogs and also we must advise a secondary contraceptive methods.

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