The Breast (2007) **16**, 323–325

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THE BREAST

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CASE REPORT

Potential benefit of maintenance trastuzumab and anastrozole therapy in male advanced breast cancer

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Received 28 September 2006; received in revised form 11 November 2006; accepted 18 December 2006

KEYWORDS
Male breast cancer;
Fulvestrant;
Anastrozole;
Trastuzumab

Summary Less than 1% of breast cancers occur in males, and the optimal hormonal therapy in this setting is unknown. Tamoxifen is effective in this entity, but unfortunately there is little information on aromatase inhibitors (AI) or fulvestrant. It has been suggested that the association of AI and GnRh analogues and AI could block the two routes of oestrogen production in males, and therefore this approach could increase efficacy. However, it could also enhance the rate of adverse events (hot flashes, sexual impotence, etc.). In this report we report 11 months of progression-free survival, without any adverse events, in a patient who received trastuzumab and anastrozole therapy. We conclude that this combination is a reasonable option in men with ER+ and Her2+ advanced breast cancer.

Introduction

Male advanced breast cancer is an uncommon entity. For this reason, the optimal hormonal therapy remains unclarified in randomised clinical trials, and conclusions are frequently extrapolated from female studies.

Tamoxifen is effective in this entity[1]; however, there is little information on aromatase inhibitors (AI) or fulvestrant. It has been recently proposed that the combination of GnRh analogues and AI might be the optimal approach, as it blocks the two main sources of oestrogen production in males.[2] However, these schemes are not exempt from side effects such as hot flashes or sexual impotence.

Otherwise, in the subgroup of both Her2 and oestrogen-receptor positive (ER+), the association of AI and trastuzumab is very attractive, because its activity and tolerability have been demonstrated in female patients.[3] However, clinical outcome with this combination had not been previously reported in male advanced cancer.

In this article, we report the clinical result of the combination of anastrozole and trastuzumab in this

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doi:10.1016/j.breast.2006.12.010

setting. We sustain the hypothesis that the combined inactivation of both Her2 and oestrogen pathways is synergistic in male patients with a safe toxicity profile.

Case report

A 40-year-old man, diagnosed in July 2004 with AJCC stage IIB (pT2pN1Mx) breast cancer, with ER+ and Her2/neu positive (IHC 2+, FISH +), was initially treated with modified radical mastectomy. The work-up consisted of CBC, liver function test, alkaline phosphatase, chest X-rays, and abdominal ultrasound. The family history was also negative. The patient did not complain of skeletal symptoms, but during the early postsurgical period, he suffered spinal cord compression due to D8 metastases. He received vertebral radiotherapy (30 Gy) with complete recovery, and sequential chemotherapy with epirubicin and cyclophosphamide (EC), with progressive disease after five courses (multiple lung and liver metastases). The reason for starting EC was that immunohistochemistry (IHC) for HER2/neu was positive (2+). At that time, we sent samples for FISH test to a centralised laboratory, but this procedure was delayed somewhat. We received the positive result in November 2004.

Second-line chemotherapy with docetaxel and trastuzumab (Herceptin; Genetech) was started, showing a complete response of the lung metastases, and partial remission of the liver lesions. In April 2005, the patient began anastrozole (Arimidex; AstraZeneca) and trastuzumab maintenance therapy with 11 months complete remission and an excellent quality of life. These drugs were continued until March 2006, when liver progression was detected. He then received fulvestrant (Faslodex; AstraZeneca) and trastuzumab for 4 months with stable disease, but experienced distressing hot flashes. In July 2006, liver progression was observed again and weekly paclitaxel (Taxol; Bristol) and capecitabine (Xeloda; Roche) were initiated.

Discussion

Less than 1% of breast cancers occur in male patients, and therefore the optimal therapy is frequently extrapolated from randomised studies of women. However, due to sexual dimorphism, the most adequate hormonal strategy remains unknown.

Approximately 90% of male breast cancers are ER+, but in contrast, the rate of Her2 overexpression is only about 5%. Tamoxifen is effective in this entity, but unfortunately there is little information on AI or fulvestrant.

In men, 80% of estrogens come from peripheral aromatisation of circulating androgens (Δ^4-androstenedione to estrone, and testosterone to estradiol), and only 20% are produced directly by the testes. For that reason, there is some preoccupation with the possibility that AI might constitute a suboptimal strategy in male breast cancer, as occurs in premenopausal women.

Anastrozole reduces estrogens by 80% in postmenopausal women. In healthy males, it is only able to diminish estradiol levels by 50%, but the loss of feedback increases gonadotropins and testosterone (aromatase substrate). A similar effect is also observed in premenopausal women treated with AI, with estradiol reductions of 39% and a parallel increase in FSH.

Although some reports have claimed two objective responses with AI, other communications have only reported stabilisations between 4 and 9 months.[4] It has been suggested that the association of GnRh analogues and AI might block the two routes of oestrogen production in males, and therefore this approach may increase efficacy.[5] However, it may also enhance the rate of adverse events (hot flashes, sexual impotence, etc.). In our patient, maintenance therapy with trastuzumab and AI provided almost 1 year of progression-free survival, without apparent toxicity, and with excellent quality of life. We think these results were probably not the consequence of favourable tumour biology, because of its initial aggressive behaviour and refractoriness to anthracyclines. The change from anastrozole to fulvestrant provided another 4 months of stabilisation, but with disturbing hot flashes.

The association of trastuzumab and AI has been documented in advanced breast cancer, for example, a phase II study demonstrated objective responses in 26% and clinical benefit in 52% with letrozole and trastuzumab.[2] Time to progression in this study was 5.8 months. Nevertheless, 82% of patients had received previous tamoxifen. Interestingly, anastrozole as first-line therapy showed a clinical benefit rate of 59%, and a TTP of 11.1 months when only 12% of patients had received previous tamoxifen.[3] Although there are no a randomised trials directly comparing AI plus trastuzumab with trastuzumab alone, the reported overall response rate and TTP for trastuzumab monotherapy seems to be lower. In addition, it has been recently suggested that the Her2 pathway is involved in resistance to hormonotherapy phenomena, through paracrine or autocrine mechanisms that promote cell growth,

which translates into less effectiveness in Her2-positive patients receiving hormonotherapy alone. For example, the TAnDEN trial has compared trastuzumab and anastrozole versus anastrozole alone as first-line therapy for advanced breast cancer. The response rate (20% versus 6.8%) and TTP (4.8 versus 2.4 months) were improved in the group receiving combination therapy. Furthermore, some reports have insinuated that trastuzumab therapy might induce the reappearance of oestrogen receptors in tumours that had lost expression of these during previous therapy.

Therefore, we conclude that the combination of AI and trastuzumab after aggressive chemotherapy is a reasonable option in men with ER+ and Her2+ advanced breast cancer.

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