Durable clinical benefit with exemestane in leptomeningeal metastasis of breast cancer

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Since most chemotherapy agents do not cross the blood brain barrier, the classical approach for leptomeningeal metastasis (LM) of breast cancer is the administration of cranial intra-ventricular chemotherapy. The roles of hormonal agents like tamoxifen and aromatase inhibitors in LM treatment are not clear. We report the case of a patient with leptomeningeal metastasis from breast cancer with long-term stabilisation using exemestane. Although the ideal therapy for LM remains under debate, hormonal therapy can contribute towards maintaining the response in some patients with LM and hormone-positive breast cancer.

Key words: exemestane, leptomeningeal metastasis, breast cancer

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INTRODUCTION

Metastases of the central nervous system (CNS) are found in about 10-15% of breast cancer patients[1] and in up to 30% of patients at autopsy[2]. Breast cancer is the primary tumour that is most frequently associated with leptomeningeal metastasis (LM); about 2% to 5% of breast cancer patients developing leptomeningeal metastasis (LM) in the course of the clinical evolution of the disease[3, 4]. Prognosis is poor for patients with LM involvement; the median survival being 2 to 4 months[4, 5]. Standard treatment consists of cranial intra-ventricular chemotherapy combined with involved-field radiotherapy (RT) or whole-brain RT.

The incidence of CNS metastasis is on the increase due to several reasons. New treatments are prolonging the survival of breast cancer patients and, as such, extended survival despite secondary involvement becomes more common. Also, as has been well documented, most chemotherapy drugs, including the newer agents such as trastuzumab, do not cross the blood brain barrier (BBB)[6] and, additionally, current diagnostic procedures are better at characterising LM. Hence, the main objective of currently-available therapies is towards improving these conditions.

Intra-ventricular chemotherapy has several toxic effects and, hence, some practitioners do not recommend this approach so long as systemic (intravenous) chemotherapy can prolong survival adequately[4, 7]. The role of hormonal treatment, using tamoxifen and aromatase inhibitors, is not clear but several reported cases have shown benefits in terms of extended stabilisation of the disease. We report a case of a breast cancer patient with LM involvement with long-term stabilisation with exemestane. To our knowledge this is the first reported case treated with this hormone.

CASE REPORT

A 34 year old woman was diagnosed in 1990 as having an infiltrating ductal carcinoma of the left breast with positive axillary lymph nodes and positive hormonal receptors. She underwent breast conserving surgery and axillary node dissection followed by adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil plus adjuvant radiotherapy and with tamoxifen prescribed for 5 years. Relapse with liver metastases occurred 10 years after diagnosis. Fine-needle aspiration showed tissue HER2 over-expression. A combination of paclitaxel + trastuzumab was administered for 8 months with stable disease as outcome. Paclitaxel was discontinued and, with menopausal status confirmed, the patient continued treatment with anastrozol + trastuzumab. In August 2001 liver disease progression was observed. Anastrozol and trastuzumab were discontinued and second-line chemotherapy with docetaxel + epirubicin was ad-

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ministered. The outcome was partial response. Six months later she experienced headache, nausea and gait disorder. Magnetic resonance imaging (MRI) revealed possible leptomeningeal metastasis, but cerebrospinal fluid (CSF) analysis was tumour negative. Treatment with corticoids and oral etoposide induced a resolution of her neurological symptoms, so treatment with etoposide was continued. In January 2003 the headaches, nausea and ataxia returned. A new CSF analysis revealed the presence of tumour cells and the MRI confirmed leptomeningeal progression of the disease. The patient received intra-thecal methotrexate initially and then the etoposide was continued. In November 2003 etoposide was discontinued because of toxicity, but with stable disease.

Treatment with exemestane was commenced as single therapy and continued for 12 months. There was no progression of the disease, an absence of neurological symptoms and with normal CA-15.3 level. After 12 months of treatment the patient presented with disease progression which was confirmed by MRI. Although intra-thecal methotrexate and systemic chemotherapy was reintroduced, she finally died due to LM progression.

DISCUSSION

The classical approach for LM treatment is the administration of cranial intra-ventricular chemotherapy since most chemotherapy drugs do not cross the BBB. Several studies have demonstrated that meningeal tumour deposits are well vascularised with highly permeable blood vessels[8]. Also, some studies have demonstrated that patients with breast cancer may respond to systemic chemotherapy[5, 7]. It has been well documented that LM can alter the normal flow of the cerebrospinal fluid (CSF) and reduces the spread of the intra-ventricular chemotherapy into the LM[9]. In addition, metastases can disrupt the BBB and allow the penetration of chemotherapy or hormone therapy agents which, under normal circumstances, do not cross this barrier.

The role of hormonal agents such as tamoxifen and aromatase inhibitors in the treatment of LM is still unclear. Tamoxifen is a lipophilic agent that can penetrate the BBB easily and, indeed, several cases of LM of breast cancer responding to tamoxifen have been reported[10]. Also, tamoxifen has shown some activity in several series of patients with brain metastasis[11-14]. The absence of pharmaco-kinetic data on aromatase inhibitors (AI) penetration into CSF confirms the scepticism of some members of the oncology community regarding the potential of these agents to be effective in the treatment of LM. To the best of our knowledge, AI has been reported in only 2 cases, to-date. One case was of a patient treated initially with tamoxifen and subsequently with anastrozol, with neurological response of 12 months duration being achieved[9]. The other case was of a patient treated with letrozol, with a progression-free survival period of 16 months[15].

As such, the present case represents the first case report of an extended duration of stable disease in LM breast cancer metastasis treated with exemestane. This drug differs from other 3rd generation aromatase inhibitor in that its effect is non-reversible. Also, especially because of its steroidal structure, it is more lipophilic and which accounts for its better penetration through the BBB.

In our opinion, in postmenopausal women with hormone-positive breast cancer tumours and leptomeningeal metastasis, exemestane could, in absence of rapidly progressive visceral disease, contribute to maintaining the response in LM following intra-thecal and/or systemic chemotherapy. Our case report challenges the notion of LM as a hormone-refractory condition and suggests that hormone receptor status, rather than anatomical site, should be the preferred criterion when considering the benefit of administrating a hormonal therapeutic scheme for this condition.

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