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Newly diagnosed breast cancer in a patient receiving imatinib mesylate

ABSTRACT

Imatinib mesylate is the standard treatment of chronic myeloid leukemia (CML). Despite imatinib is being used in the treatment of other malignancies as well, its potential role on de novo tumor growth is not known. Secondary malignancies are rarely seen in patients with CML and particularly in those receiving imatinib. Here, we present a CML patient taking imatinib therapy that was diagnosed to have breast cancer and received adjuvant chemo-and radiotherapy with imatinib. We tried to explain co-occurrence of these rare events by probable pathogenetic mechanisms.

KEY WORDS: Breast cancer, chronic myeloid leukemia, imatinib

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INTRODUCTION

Imatinib mesylate has become the first-line treatment in the management of chronic myelogenous leukemia (CML). It targets abl, kit, and platelet-derived growth factor receptor protein tyrosine kinases, which are involved in cellular signal transduction and various cellular processes such as proliferation, cell migration, differentiation, and survival. In clinical practice, it has been used successfully for the treatment of Philadelphia (Ph)–positive acute lymphoblastic leukemia, c–kit positive gastrointestinal stromal tumors, and hyper eosinophilic syndrome as well.[1] Secondary malignancies can be seen in the course of CML, but it is very rare.[2] There are speculative data showing that the imatinib may have the potential to induce certain types of tumors.[3] To the best of our knowledge, this is the first report of breast cancer that developed during imatinib treatment in a patient with CML.

CASE REPORT

A 46-year-old woman was diagnosed to have Ph–positive CML in our out-patient clinic. Imatinib was started at a dosage of 400 mg once daily on June 2003. 6 months later, cytogenetic and molecular remission was achieved. She found a mass in her left breast on April 2005. Ultrasonography confirmed a solid, hypoechoic, heterogeneous, and ill-defined mass. Fine-needle aspiration was performed and invasive ductal carcinoma diagnosis was made by pathological examination. A left modified radical mastectomy was performed. Pathology revealed an invasive ductal carcinoma of 1.5 cm in size (T_1), grade 1, estrogen receptor-negative, progesterone positive, and 1 out of 14 lymph nodes was positive (N_1). Her metastatic work-up showed no evidence of disease spread (M_0). Her CML was still in complete hematological, molecular, and cytogenetic remission.

She was started on adjuvant chemotherapy with cyclophosphamide 600 mg/m^2 and epirubicin 90 mg/m^2, given every 21 days for 4 cycles. She also continued her imatinib therapy without any dose modification. The patient developed neutropenia on the 13th day of the first cycle of chemotherapy. Imatinib was discontinued for a week, and doses of both chemotherapy drugs were reduced by 10%. After recovery of neutrophil count, imatinib treatment was resumed at a lower dose of 300 mg per day. The patient completed chemotherapy without any other side-effects.

On August 2005, she was started on tamoxifen 20 mg/day p.o. and radiotherapy for N_1 disease. She was treated with a total of 6000 cGy for 59 days according to our center's protocol. She was able to receive imatinib therapy during adjuvant treatment. No other adverse events were observed except one febrile neutropenic episode. Her renal and liver function tests remained within normal limits. After completing radiotherapy, imatinib dose was again increased to 400 mg/day. The patient is still in complete remission on imatinib and under tamoxifen therapy.

DISCUSSION

Annual incidence of CML and breast cancer is about 1-2 and 127 cases per 100 000 patient per

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year, respectively.[1,4] Coincidence of CML and secondary malignancies are rare and unusual occurrence with very few previously reported cases. Besides, coincidentally diagnosed cancers under imatinib therapy were also rarely reported.[5]

When the patient was diagnosed to have breast cancer, she was receiving only imatinib; she had not taken any form of medication, which may be a potential causative risk factor for malignancy before or during treatment. There was no family history of breast cancer, and she was a premenopausal, multiparous woman with no known traditional breast cancer risk factors. Considering the relative frequency of breast cancer, CML, and very low incidence of secondary malignancies in patients receiving imatinib, we think that coincidence of more than one rare event cannot solely be explained just by chance.

Recent studies have raised concerns that imatinib could cause secondary tumor growth. The EphB4 receptor is a transmembrane tyrosine kinase. Ephrin-B2 ligand binds to this receptor and stimulates EphB4 receptor kinase activity and downstream signaling in cells. Noren *et al*. showed stimulation of EphB4 tyrosine kinase by ephrin B2 ligand inhibits cell growth, survival, migration and invasion, which results in tumor suppression. In this study it was also shown that this tumor suppressor pathway is related to abl kinase. Inhibition of EphB4-Ephrin B2 pathway by imatinib may cause malignant transformation of the breast epithelial cells.[3] In addition, imatinib may have an anti-apoptotic effect on some cancer cells including melanoma and prostate cancer by interfering with caspase activation.[6]

Imatinib causes reversible and antigen-presenting cell–independent inhibition of T-cell activation and proliferation at *in vitro* concentrations those can be achieved by therapeutic *in vivo* doses. However, it does not induce apoptosis. This is associated with a reduced primary cytotoxic t-lymphocyte response. Since T-cells derive from Ph–negative clone, reports of malignancies under imatinib was attributed to imatinib use rather than the presence of CML.[7]

In vitro, imatinib causes increased motility of the surviving cells and overexpression of tumorigenic genes related with invasive behavior in breast cancer cell lines. *In vivo*, mice implanted with breast cancer develop more tumors under imatinib. Rappa *et al*. suggested that imatinib induces a gene expression profile, which is associated with aggressive tumor biology. It also facilitates tumor engraftment by means of its immunosuppressive effects.[8]

Retrospective analyses of patients with CML receiving tyrosine kinase inhibitors (TKIs) reported similar or even decreased incidence of secondary malignancies in comparison to a healthy population.[9] However, some have short follow-up, and others reported combined analysis of all TKIs.

Although this possible pathogenetic mechanism does not exclusively prove that coexistence of both diseases in this patient was not coincidental, and some preclinical studies showed anti-tumor activity of imatinib on malignancies as well as on breast cancer, this case reveals a need for a long-term safety study assessing the effect of imatinib on *de novo* tumorigenesis.[10]

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