Concomitant Use of Ado-trastuzumab Emtansine and Imatinib in a Patient of CML and Metastatic Breast Cancer

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ABSTRACT

Imatinib is a CYP3A4 inhibitor, while ado-trastuzumab is a CYP3A4 substrate. Imatinib can interact with ado-trastuzumab emtansine (T-DM1) and can increase T-DM1 concentrations, leading to T-DM1-related toxicity. There is no trial or case report in the literature on the concomitant use of Imatinib and T-DM1. Herein, we report a case in which T-DM1 was used effectively with imatinib in a patient with chronic myeloid leukaemia (CML) and metastatic Her-2-positive breast cancer. A 37-year female using imatinib for CML was diagnosed with breast cancer and a modified radical mastectomy was performed. Skin metastasis occurred within one year after adjuvant therapy was completed. Lung metastasis occurred after Trastuzumab + vinorelbine treatment and T-DM1 and imatinib were given to the patient. No side effects were observed except for grade 1 fatigue. This case report is the first to report the concomitant use of T-DM1 and imatinib in a patient of CML and metastatic breast cancer.

Key Words: *Imatinib, Ado-trastuzumab emtansine, Breast cancer, Chronic myeloid leukaemia.*

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INTRODUCTION

As one of the game-changer treatments in chronic myeloid leukaemia (CML), imatinib is still used effectively as the first-line treatment and the chronic phase of the disease.[1] Pretibial-periorbital oedema, myalgia, and fatigue are common side effects of imatinib.[2]

Trastuzumab emtansine (T-DM1) is a conjugate composed of a combination of trastuzumab that targets the Her-2 receptor and a maytansine derivative (DM1, a microtubule inhibitor).[3] T-DM1 has been shown to improve survival in metastatic Her-2-positive patients who have previously received trastuzumab and taxane therapy[4]. Nausea/vomiting, fatigue, diarrhoea, and thrombocytopenia are common side effects of T-DM1.[4]

Imatinib is a CYP3A4 inhibitor, while ado-trastuzumab is a CYP3A4 substrate. Imatinib can interact with T-DM1 and can increase T-DM1 concentrations, thereby leading to T-DM1-related toxicity. Herein, we report a case in which T-DM1 was used effectively with imatinib in a patient with CML and metastatic Her-2 positive breast cancer, which has never been reported in the literature.

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CASE REPORT

A 37-year female, who has been followed up with CML since 2013 and was in molecular remission with imatinib, was referred to surgery due to the mass in the right breast and axilla. Physical examination and breast ultrasonography (USG) revealed a 2 cm mass in the right breast and a 2.5 cm lymphadenopathy (LAP) in the right axilla. The patient was diagnosed with hormone receptor-positive (HR +) and Her-2-positive breast cancer on biopsy. The postoperative stage of the patient undergoing right modified radical mastectomy was T2N3M0. Trastuzumab treatment was completed for 1 year after the patient received 4 cycles of adjuvant adriamycin + cyclophosphamide (AC), and 12 weeks of paclitaxel + trastuzumab therapy. The patient underwent radiotherapy after adjuvant chemotherapy (CT) and LHRH analogue and tamoxifen were also initiated. Skin metastasis occurred within one year after adjuvant therapy was completed. The biopsy result was compatible with HR + and Her-2 + breast carcinoma. Lung metastasis occurred after a total of 18 cycles of trastuzumab + vinorelbine in the patient who did not have other distant metastases. The patient, who continued imatinib throughout this period, was still in major molecular remission for CML. We started T-DM1 treatment for the patient who developed progression after trastuzumab + vinorelbine. No side effects were observed except for grade 1 fatigue. The patient, who had stable disease, received a total of 15 cycles of T-DM1 with imatinib and the treatment is still going on.

DISCUSSION

Imatinib can increase CYP3A4 by 2-3.5-fold. Therefore, imatinib can interact with drugs metabolised by these enzymes.[5] Imatinib

is a CYP3A4 inhibitor while ado-trastuzumab is CYP3A4 substrate, implying that imatinib has the potential to increase ado--trastuzumab concentrations and thereby can lead to ado-trastuzumab related toxicity.[5]

To the best of our knowledge, there is no data in the literature on the concomitant use of Imatinib and T-DM1. The number of cases or studies in which Imatinib and chemotherapy are used together is very limited.[6,7] Samal *et al*. demonstrated the efficacy of using low-dose cytarabine and imatinib together in patients with CML in their prospective randomised controlled trial[6]. In this study, although Grade 3/4 neutropenia, thrombocytopenia, anaemia, and nausea were more common in the combination therapy cohort compared to the monotherapy (imatinib alone) cohort, patients were generally able to tolerate combined therapy.[6]

Fazio *et al*. arranged a concomitant use of imatinib and CT to a patient with acute lymphoblastic leukaemia and published as a case report.[7] Because of the poor response to CT, they used imatinib with cytarabine and fludarabine for approximately 7 weeks.[7] They did not observe any serious toxicity during this period.[7]

The possibility of imatinib interaction with other drugs metabolised by CYP3A4 and CYP3A5 enzymes may worry clinicians. Hence, Tatsuka *et al*. stopped imatinib for a 6-month period in a patient with known CML and receiving adjuvant chemotherapy for colon cancer.[8] They avoided combined use due to possible potential interactions and side effects of imatinib and CT.[8] Clinicians may not always be lucky to encounter cases in which they can take a break from one of the treatments. So, they may have to apply combination treatments with caution like in this case. We did not observe any significant side effects except grade 1 fatigue in the patient who received T-DM1 and imatinib for metastatic Her-2 + breast cancer and CML.

In conclusion, we have demonstrated with this case that T-DM1 and imatinib may be used together with caution. However, clinical trials are needed for precise information on the safe usage of these two agents together.

PATIENT'S CONSENT:
Informed consent was obtained from the patient to publish this case report.

COMPETING INTEREST:
The authors declared no competing interest.

AUTHORS' CONTRIBUTION:
CK: Manuscript writing.
IB: Patient recruitment.
FBB: Data collection.
OBO: Proofreading.
All the authors have approved the final version of the manuscript to be published.

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