



Medical Treatment with Two Targeted Therapies for an Oncology Patient with Double Primary Cancer: Case Report

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SUMMARY

While multiple primary tumors are rarely reported in literature, we expect that it will be seen more often in the future as a result of improvements in diagnosis and treatment of cancer. Molecular targeted therapies are promising modalities that are now used more commonly. Presently described is oncological response for a 70-year-old women with multiple primary cancers - breast and lung - in which 2 targeted therapies were administered. While there is currently no standard therapy in the literature for multiple primary cancers, it is the authors' suggestion that targeted therapies may be a promising choice for these cases.

Keywords: Invasive ductal carcinoma; lung adenocarcinoma; multiple primary cancer; targeted therapies.

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Introduction

The term multiple primary malignant tumor (MPMT) was first used by Billroth in 1889 and was first described in a report by Warren and Gates in 1932. The criteria developed by Warren and Gates to make a diagnosis of MPMT include the following: each of the tumors must be of different histological type and possibility of metastasis must be excluded.[1] MPMTs are divided into 2 groups, synchronic and metachronic. If a second primary tumor is diagnosed within the first 2 months after the diagnosis of first primary, it is called synchronic. If more than 2 months have elapsed when the second primary is diagnosed, the term metachronic is used.[2] The incidence of MPMTs is reported to be in the range of between 0.4% and 21.0% in different countries and various studies.[3-6]

Currently, survival of cancer patients is increasing due to both improvements in treatment modalities

and availability of early diagnosis; thus, there will be an increasing need for management of multiple tumors in future. The mechanisms that cause MPMTs are still unclear. While genetic predisposition can play an important role in these cases, such as with hereditary non polyposis coli syndrome, which increases risk for ovarian, endometrial and small intestine cancers as well as colon carcinoma, intensive use of chemotherapy and radiotherapy (RT) might be also associated with certain types of primary cancers.[7-10]

In the last quarter of the 20th century, improvements in hybridoma and recombinant DNA technologies led to use of monoclonal antibodies (mAb) for diagnosis *in vitro* and *ex vivo*, and subsequently they have been included in clinical use as a treatment option. Within 30 years, mAb therapy has become part of standard treatment for certain types of cancer.[11]

Targeted cancer therapies are drugs designed to interfere with specific molecules necessary for tumor

growth and progression. Traditional cytotoxic chemotherapies usually kill rapidly dividing cells in the body by interfering with cell division. A primary goal of targeted therapies is to fight cancer cells with more precision and potentially fewer side effects.[12]

Many different targeted therapies have been approved for use in cancer treatment. These include hormone therapies, signal transduction inhibitors, gene expression modulators, apoptosis inducers, angiogenesis inhibitors, immunotherapies, and toxin delivery molecules.[13]

In terms of studies observing treatment of MP-MTs, Zeng et al. investigated hepatocellular carcinoma (HCC) tumors accompanied by non-HCC primary tumors and reported that it was important to treat both the synchronic and metachrone tumors, while also pointing out need for additional studies to support their observations.[14]

Search of literature revealed no reports in which more than one targeted therapy was administered for multiple primary tumors. Described in the present case is multiple primary carcinoma – primary lung cancer and ductal invasive breast carcinoma – along with liver metastasis for which targeted therapies for both lung and breast cancer were administered.

Case Report

A 70-year-old woman presented at internal medicine outpatient clinic with complaints of fever, weight loss, and breathlessness. Following lung X-ray that showed suspected tumor signs, computed tomography (CT) was performed. Tumors were found in multiple lymph nodes - max. 10x5 mm - in prevascular and aorticopulmonary sites, bilateral hilus and precarinal sites, and a centrally located mass with irregular margins, 38 x 25 mm in size, was found at the lower lobe of right lung. Diagnosis of adenocarcinoma was made with bronchoscopic biopsy. Mutation of activin receptor-like kinase 1 gene (ALK1) was negative while epidermal growth factor receptor (EGFR) was positive. Positron emission tomography (PET) was performed for staging. Apart from lymphadenopathy seen in CT, hypermetabolic mass lesion suggesting metastasis at segment 7 of the liver, hypermetabolic lymphadenopathy at hepatic hilus, and focal hypermetabolic lesion 10 mm in diameter in upper middle quadrant of right breast were found, suggesting secondary primary. In addition, bone metastasis located at first thoracic vertebra, right iliac bone and right ischium was detected. Tru cut biopsy of the breast showed invasive ductal carcinoma.

Immunohistochemically estrogen and progesterone receptors were found to be >%90 positive, and c-erb-B2 (HER2/neu) was found to be strongly positive. As the patient was evaluated as multiple primary, biopsies of liver metastasis to determine primary was planned; however, approval of the patient could not be obtained for biopsy. Before announcement of results of immunohistochemical and genetic testing, 4 cycles of chemotherapy with paclitaxel 250 mg, carboplatin 600 mg and zoledronat 4 mg were administered every 3 weeks. After chemotherapy, a partial metabolic regression in lesion located in lower lobe - posterobasal segment of left lung - a complete regression in lymphadenopathies located in right lower paratracheal site, and complete regression of mass in right breast was obtained. Furthermore, metastatic mass lesion observed initially in segment 7 of liver was not reported. Since EGFR was positive in lung adenocarcinoma and c-erb was positive in breast adenocarcinoma immunohistochemically, maintenance treatment was as follows: erlotinib 150 mg/day, letrozole 2.5 mg/day, trastuzumab 520 mg loading dose followed by 420 mg was continued for 12 cycles every 3 weeks. At ninth month of treatment, patient was still in follow-up, with assessment of stable disease according to the Response Evaluation Criteria In Solid Tumors (RECIST) version 1.1.[15]

Discussion

While there is no data regarding administration of both erlotinib and trastuzumab for patients with double primary lung and breast cancers in literature, there are a few case series of administering c-erb targeted treatments to HER2 positive patients as phase I/II studies. [16] These drugs were well tolerated in our study, and there no drug interactions were found in databases. Administration of these 2 targeted therapy modalities in patients with HER2 positive breast cancer was still in progress at the time of present case and there is no data regarding use of more than one targeted therapy in patients with metastatic multiple primary cancer.

In a study investigating outcomes of synchronic non-small cell lung cancers, it was shown that best outcomes can be obtained with more than 1 targeted therapy if tumor is resectable; however, these synchronic tumors were only tumors originating in the lung.[17] In the present case, patient was evaluated as non-resectable due to liver metastasis, primary nature of which could not be clarified because patient did not give approval for biopsy.

In literature, outcomes of multiple primary cancers

that were accompanied by lung cancer have been investigated.[18–20] In a study conducted by Li et al., it was reported that the most common cancers to exist concurrently with lung cancer were of digestive system; breast cancer was included in the group of “others,” which compromised 9.7% of total.[21] However, another study reported that concurrence of lung and breast cancer made up highest percentage for both metachrone and synchronic groups of patients with multiple primary tumors.[22]

Most side effects of targeted therapies are directly related to the specific molecular target in normal tissue inhibited or modulated by the specific drug. As present case involves administration of 2 targeted therapies, potential side effects of both were considered. The most commonly observed side effect with EGFR inhibitors is an acneiform eruption, also called acne-like rash or folliculitis, which occurs in 50% to 100% of patients.[23–25] Acneiform eruption is less frequent with erlotinib compared to cetuximab or panitumumab.[26]

Post-chemotherapy diarrhea is the result of extensive crypt damage in the small bowel and colon, resulting in excess fluid in the bowel lumen. Exact pathophysiology of anti-EGFR agent-related diarrhea remains unclear. EGF is involved in the maintenance of mucosal integrity and is also a potent mitogen of the gastric epithelium; it stimulates mucin production and enhances prostaglandin synthesis.[27,28] In the present case, neither skin toxicity nor intestinal toxicity was experienced with erlotinib treatment.

Trastuzumab was humanized from the original mAb, thereby allowing chronic administration in humans without development of human anti-mouse antibodies response, which is characterized by anaphylactic response or other immune reactions and rapid drug clearance.[29] Approximately 40% of patients receiving trastuzumab experience some degree of infusion-related symptoms such as a flu-like syndrome that includes fever and chills, mainly during the first infusion. Other common reactions include tumor site pain, shortness of breath, muscle weakness, cutaneous rash, diarrhea, and headache. Trastuzumab is administered intravenously over 90 minutes for the first infusion with a primary line of saline solution. If first infusion is well tolerated, subsequent doses can be administered over 30 minutes.[26] One major concern is cardiac toxicity related to trastuzumab administration. Cardiac dysfunction was specifically defined as follows: cardiomyopathy characterized by decrease in left ventricular ejection fraction (LVEF), either global or more severe in the septum; symptoms of congestive heart failure

(CHF); associated signs of CHF; decline in LVEF of at least 5% to <55% with signs and symptoms of CHF; or a decline of 10% to <55% without signs or symptoms of CHF. Trastuzumab is associated with increased risk of cardiac dysfunction, which is greatest in patients receiving concurrent anthracyclines.[30]

In the present case, echocardiogram was performed at initiation of therapy. LVEF was initially 60% and there was no decrease seen during or after treatment.

It is clear that resectability and adverse effects can create difficulties in treatment of multiple primary tumors. However, targeted therapies are developing rapidly and there are promising reports that these modalities will be widely used in the near future. Since there is no definitive modality for treating patients with multiple primary tumors at this time, it is the suggestion of the authors that treatments targeting the same pathways to hit the tumor could be a promising choice of treatment. In the present case, we obtained a better survival than expected with 2 targeted therapies. The result must definitely be supported by further studies in terms of drug interactions and side effects.

Conflict of interest: None declared.

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