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Journal

BMJ Case Reports, 2014(jun04 1)

ISSN

1757-790X

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Publication Date

2014-06-04

DOI

10.1136/bcr-2013-203400

Peer reviewed

CASE REPORT

Metastatic human epidermal growth factor 2 (HER2/neu) amplified breast cancer with acute fulminant hepatitis responding to trastuzumab, pertuzumab and carboplatin

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Accepted 9 May 2014

SUMMARY

A 30-year-old woman presented to an outside hospital with pain in the right upper abdomen. Imaging revealed over 100 liver lesions, the largest measuring 74 mm×71 mm, and multiple lytic bone lesions. An outpatient liver biopsy showed a poorly differentiated adenocarcinoma favouring a breast primary. The tumour was oestrogen and progesterone receptor negative, but human epidermal growth factor 2 (HER2/neu) amplified. In her second clinic visit she had decompensated liver failure manifested by new-onset ascites and jaundice. Initially, the chemotherapy plan was for docetaxel, pertuzumab and trastuzumab, but given her severe liver dysfunction we used a combination of carboplatin, pertuzumab and trastuzumab as an inpatient. She was hospitalised for 14 days and eventually discharged with a marked improvement of her symptoms and liver tests. She subsequently completed five outpatient chemotherapy cycles. We showed that carboplatin is a possible alternative to docetaxel when severe liver dysfunction precludes docetaxel's use in combination with pertuzumab and trastuzumab.

BACKGROUND

Breast cancer is the second leading cause of cancer deaths and the most common malignancy in women,[1] and cure is usually unachievable in the metastatic setting. About 20% of breast cancers are human epidermal growth factor 2 receptor (HER2/neu) amplified and present in more advanced stages in younger women with a more aggressive clinical course.[2 3] About 30% of HER2/neu-positive breast cancer cases present as metastatic disease and cytotoxic chemotherapy along with targeted anti-HER2/neu therapy is indicated as first-line therapy.[4] Trastuzumab, a humanised murine HER2/neu antibody, has altered the prognostic outcome of patients with HER2-amplified breast cancer and has resulted in prolonged overall survival.[5] Single-agent trastuzumab has a response rate of about 20% which increases to over 50% when given in combination with cytotoxic chemotherapy with clinical benefit lasting approximately 10 months.[3 6]

It has been reported that 30–50% of patients with breast cancer will have liver metastasis during their disease course and patients may present with liver metastasis at the time of initial diagnosis with median survival ranging from 1 to 14 months depending on the degree of liver dysfunction.[7–10] Liver metastasis most commonly occurs in middle-aged women with ductal carcinoma histology.[10 11] Clinically, patients usually present with anorexia, encephalopathy, jaundice, markedly elevated liver function tests and no radiographic evidence of cirrhosis.[8 12 13] Acute liver failure due to liver metastasis of a solid malignancy has a dismal prognosis with a rapid and aggressive decline leading to death usually in less than 30 days.[13 14] These patients are usually treated with supportive care, and systemic chemotherapy is challenging given the impaired liver function. Our case report illustrates that in patients with HER2/neu amplification and severe liver dysfunction, urgent initiation of therapy with HER2/neu-targeted therapy and chemotherapy can reverse the severe clinical course and result in an objective response. In our case report, we present a patient with acute liver failure who was successfully treated with combination of carboplatin along with dual anti-HER2/neu-targeted therapy: pertuzumab and trastuzumab.

CASE PRESENTATION

A 30-year-old previously healthy woman presented with low-grade fevers and worsening deep 'tugging' right upper quadrant abdominal pain radiating to the upper back for 2 days. She had been previously evaluated for worsening the right arm pain and swelling for 2 months which was attributed to musculoskeletal strain by an outside provider. Six months prior she had right breast serous discharge and crusting of her nipple that resolved on its own. She had no prior history of tobacco or alcohol use. Her medical and family history was notable for a history of breast cancer in her maternal grandmother and liver cancer in her grandfather.

INVESTIGATIONS

Initial laboratory work revealed normal renal function and complete blood count, but was notable for these liver test abnormalities: aspartate aminotransferase (AST) 177 U/L, alanine aminotransferase (ALT) 194 U/L, alkaline phosphatase (AP) 128 U/L, albumin 4 mg/dL, International Normalised Ratio (INR) 1.2 and total bilirubin 1.1 mg/dL. An abdominal ultrasound revealed innumerable heterogeneous liver lesions without biliary dilation. A confirmatory CT scan confirmed diffuse innumerable liver lesions with the largest one being 71 mm×74 mm and showing enhancement characteristics consistent

To cite: Macias MN, Shin DS, Ledezma B, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2013-203400

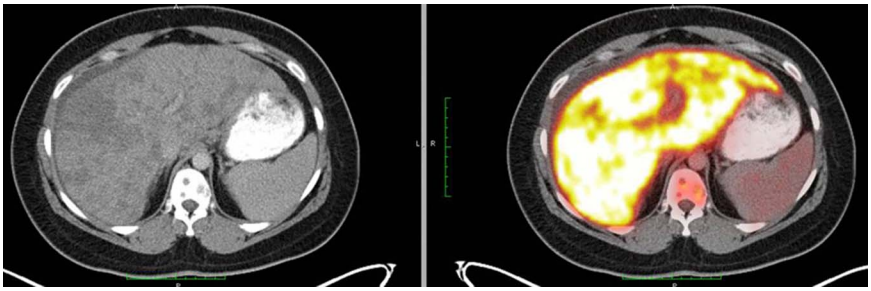

Figure 1 Positron emission tomography/CT fused image at baseline before chemotherapy showing ascites, innumerable hypodense lesions and intense fluorodeoxyglucose uptake. ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, International Normalised Ratio.

with solid neoplasm as well as thoracic, lumbar and pelvic bone lytic lesions.

Liver biopsy showed diffusely infiltrative epithelioid cells invading the hepatic parenchyma consistent with a poorly differentiated adenocarcinoma with immunohistochemistry favouring a breast primary: gross cystic disease fluid protein 15 positive, mammaglobin rare positive, thyroid transcription factor 1 negative, CK7 positive, CK 20 negative, oestrogen receptor negative, progesterone receptor negative and HER2/neu equivocal 2+. A confirmatory fluorescence in situ hybridisation for HER2/neu eventually showed amplification ratio of 7.2. Acute viral hepatitis panel was negative. A baseline positron emission tomography (PET)/CT scan showed intense fluorodeoxyglucose (FDG) uptake: in multifocal right breast lesions, subcentimeter axillary lymph node, innumerable hypodense liver lesions, axial and appendicular skeleton, portocaval and aortal caval lymph nodes (figure 1).

Since the initial presentation the patient had begun demonstrating worsening of her clinical status, namely with the development of symptoms of liver failure including pruritus and scleral icterus. The laboratory values had worsened with an increase in AST 433 U/L, ALT 286 U/L, total bilirubin 6.9 mg/dL and tumour marker CA 27-29 of 755 u/mL. The patient returned 5 days later in liver failure manifested by new-onset ascites, jaundice and worsening of liver tests: total bilirubin 13 mg/dL, AST 379 U/L, ALT 205 U/L, AP 238 U/L, albumin 2.8 mg/dL and INR 2.9.

DIFFERENTIAL DIAGNOSIS

Before the biopsy results, on the top of the differential was metastatic solid malignancies based on the radiographic description of liver lesions. Based on our case clinical presentation, a breast primary was the most likely culprit with other solid malignancies such as lung and colorectal cancer being lower in the differential.

TREATMENT

The initial plan was to start the treatment with pertuzumab, trastuzumab and docetaxel, but given her severe liver dysfunction the use of docetaxel was contraindicated. Given the patient's clinical deterioration she was hospitalised to receive inpatient chemotherapy to control her symptomatic metastatic disease with pertuzumab, trastuzumab and carboplatin. On the first day the patient received trastuzumab dose reduced to 4 mg/kg and developed a mild infusion reaction which was treated by slowing the rate and administering antihistamines and Tylenol. The patient then received pertuzumab loading dose 840 mg without complications followed by carboplatin area under curve 5. The patient received the chemotherapy over 3 days, and remained in the hospital for a total of 14 days due to worsening liver function tests with laboratory values peaking at total bilirubin 22 mg/dL, INR 4, AST 859 U/L, ALT 286 U/L and albumin 2.4 U/L (figure 2). The patient had fever with worsening ascites and had a diagnostic paracentesis showing an elevated serum-ascites albumin gradient, neutrophils >250/μL and Gram stain and cytology being negative. Based on elevated neutrophils, the patient was treated for spontaneous bacterial peritonitis with resolution of fever.

OUTCOME AND FOLLOW-UP

Subsequently, after discharge, she completed five additional chemotherapy cycles as an outpatient with trastuzumab increased to 6 mg/kg. She continued to show improvement in her liver function with subsequent normalisation of her liver tests: total bilirubin 1 mg/dL, INR 1.2, AST 25 U/L, ALT 25 U/L, albumin 3.6 U/L and CA 27–29 U/L 35 U/L. On the repeat PET/CT the patient had resolution of FDG activity in her right breast, sclerosis to spine and pelvic lesions and a marked decrease in liver densities and FDG uptake (figures 1 and 3).

DISCUSSION

Acute or fulminant hepatic failure caused by solid tumour metastasis is a rare phenomenon, accounting for only 0.44% of all cases of acute hepatic failure.[13 14] Despite this low incidence, when present, it carries a mortality rate of 90% even with treatment.[8 13 15] Given the dismal prognosis, early treatment with agents with potential for best response and tolerable safety profile is the primary goal in these cases. We presented a newly diagnosed HER2/neu-positive patient with breast cancer with massive liver metastasis and in hepatic failure who was successfully treated with a combination of carboplatin, trastuzumab and pertuzumab.

Emerging anti-HER2/neu therapies present more options to those patients that are newly diagnosed or progressed on prior targeted therapies. Advances in anti-HER2/neu-targeted therapy have been driven by the shown overall survival and quality-of-life improvement.[16] There are four Food and Drug Administration (FDA)-approved HER2/neu-targeted agents available for metastatic HER2/neu-positive breast cancer: trastuzumab (Herceptin) and pertuzumab (Perjeta) are indicated for first-line treatment, and lapatinib (Tykerb) and T-DM1 (Kadcyla) for second-line treatment. Present and ongoing studies are focusing on combining anti-HER2/neu agents, chemotherapeutics and antihormonal treatments to optimise response. Pertuzumab is an anti-HER2/neu receptor antibody which targets the extracellular domain of the transmembrane protein HER2/neu and binds to subdomain 2.[17 18] Trastuzumab on the contrary binds to subdomain 4 of the HER2/neu transmembrane protein.[17] Dual blockade of the HER2/neu receptor with pertuzumab and trastuzumab results in blockade of HER2/neu heterodimerisation.[17 18] Prevention of heterodimerisation results in inhibition of the phosphoinositide 3 kinase-driven signalling pathway and hinders proliferation of the breast cancer

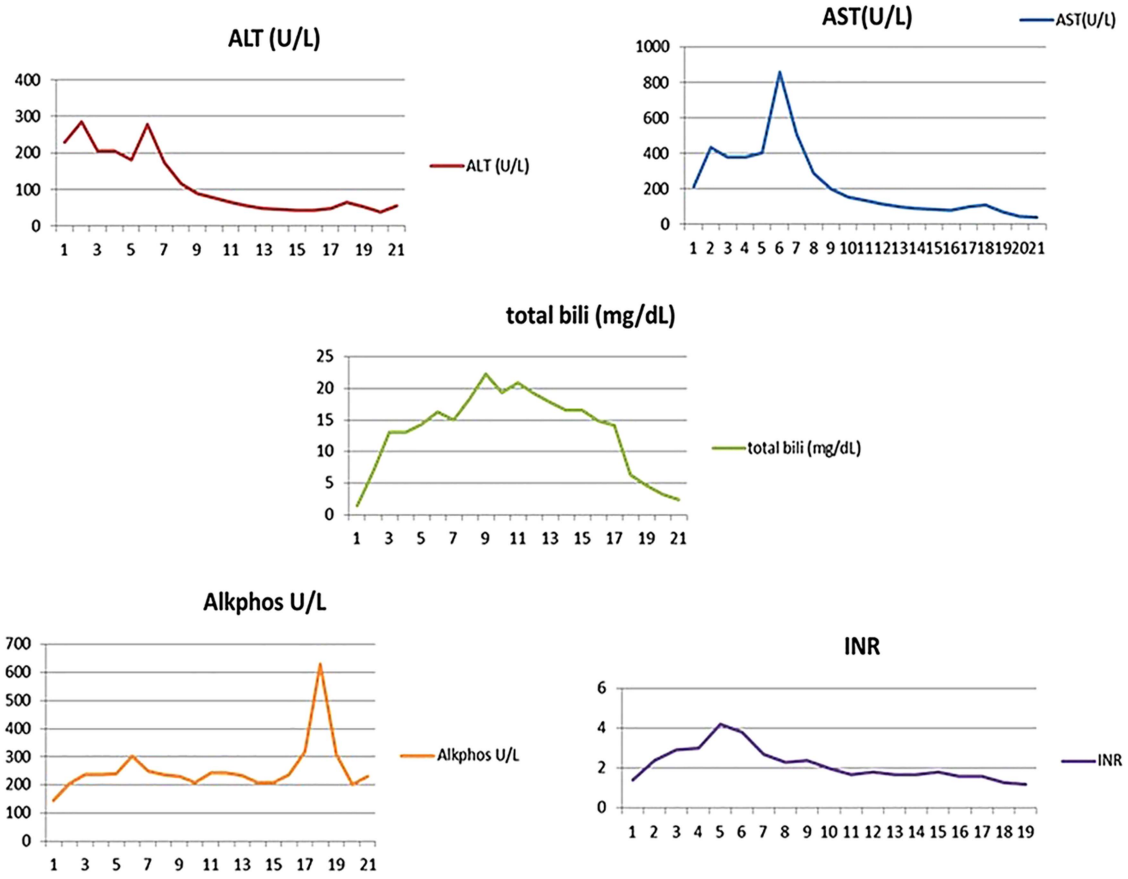

Figure 2 Laboratory values 1 week before chemotherapy and after the first chemotherapy regimen administration with carboplatin, pertuzumab and trastuzumab.

cells, which may explain the synergistic antitumour effects seen by combining pertuzumab and trastuzumab.[16 18]

Pertuzumab was approved in June 2012 as first-line therapy in metastatic HER2-positive breast cancer in combination with docetaxel and trastuzumab based on statistically significant improvement in progression free survival (18.7 vs 12.4 months) and overall survival (not yet reached vs 37.6 months) benefit.[19 20] It was also recently approved in the neoadjuvant setting for four cycles in the same combination with docetaxel and trastuzumab and showed a pathological response rate of approximately 46%.[21] HER2/neu amplification is a dominant driver of cellular proliferation in HER2/neu-positive breast cancer cells and is an independent risk factor for tumour progression and clinical outcomes such as overall survival.[5 22] Therefore, even in cases of severe organ dysfunction, potentially targeting the HER2/neu pathway may result in alteration of the dismal prognosis of these patients.

To the best our knowledge, the use of platinum cytotoxic therapy has not been documented in dual anti-HER2/neu therapy with trastuzumab along with pertuzumab. Platinum is one of the chemotherapy options known to be synergistic with anti-HER2-targeted therapy.[23] Our decision to use platinum therapy was influenced by its minimal hepatic metabolisation. Platinum therapy has been successfully used in patients with lung cancer in the setting of severe liver dysfunction with improvement of liver function and prevention of early death in 50% of the patients.[14]

Review of the literature highlighted additional case reports in which patients with metastatic breast cancer and severe liver dysfunction were treated using single-agent chemotherapy with trastuzumab, but to the best our knowledge there are no other reports of patients with severe hepatic dysfunction treated successfully with dual anti-HER2/neu inhibition and platinum chemotherapy. One case study used docetaxel in a newly diagnosed patient with breast cancer with liver metastasis and dysfunction, but unlike our patient who had a total bilirubin peak of 22.3 mg/dL, this patient had a peak bilirubin of 2.2 mg/dL.[15] In our literature search, we found two Japanese case studies on

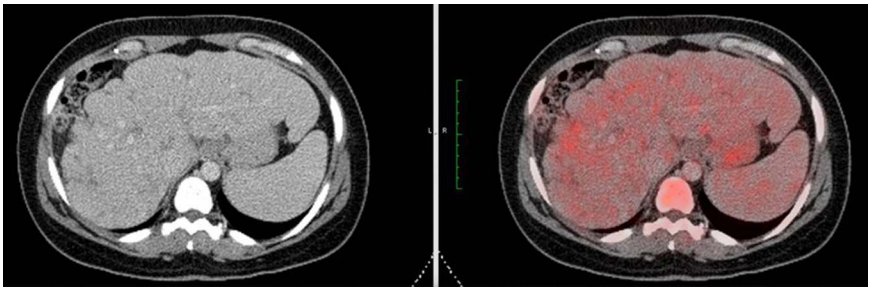

Figure 3 Positron emission tomography/CT fused image after five cycles of trastuzumab+pertuzumab +carboplatin: decreased number of visible hypodense lesions and decreased intensity fluorodeoxyglucose uptake in the liver and bone. Resolved ascites and liver contours being irregular in post-treatment images; related to treatment effect.

HER2/neu-positive breast cancer and severe liver dysfunction, with one of the cases using trastuzumab monotherapy and the other using trastuzumab and transitioning from paclitaxel to vinorelbine when severe liver dysfunction developed.[24] Another Japanese case report with liver dysfunction in HER2/neu-positive breast cancer was in the third-line setting in a patient that had progressed on trastuzumab monotherapy but responded when trastuzumab was used in combination with capecitabine.[25]

In summary, we present a case of HER2/neu-positive breast cancer with severe decompensated liver failure without prior cirrhosis that had a near complete response to the combination of carboplatin, pertuzumab and trastuzumab. Our case report shows that in patients with HER2/neu amplification and severe liver dysfunction, urgent initiation of HER2/neu-targeted therapy and chemotherapy can reverse a potentially fatal outcome. We believe that in patients with severe liver dysfunction the benefits of HER2/neu-targeted therapy outweigh the risks and should not be withheld from this critically ill patient group.

Learning points

- Solid malignancies causing severe acute liver dysfunction carry a dismal prognosis.
- In human epidermal growth factor 2 (HER2/neu) amplified breast cancer in visceral crisis the benefits of urgent initiation of targeted HER2/neu therapy outweigh the risks.
- Combinations with targeted HER2/neu therapies and chemotherapies with best therapeutic and toxicity profile can be used successfully in critically ill patients.

Contributors All the authors contributed to the literature, review, intellectual content and drafting of this paper.

Competing interests . SS declares honoraria from Roche/Genentech.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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