Reversible liver toxicity with adjuvant trastuzumab for localized breast cancer

Trastuzumab, a mAb against epidermal growth factor receptor 2 (HER2), improves survival of overexpressing HER2 metastatic [1, 2] and locoregional breast cancer [3, 4]. Except for allergic reactions and cardiomyopathy, nearly no other severe adverse events have been reported with trastuzumab monotherapy [3–6]. We present here one patient who suffered grade 4 reversible liver cytolysis after the loading dose of trastuzumab for the adjuvant treatment of localized breast cancer.

A 31-year-old Caucasian healthy woman underwent lumpectomy and lymphadenectomy for a grade 2, node-negative, hormone receptor-negative, ductal carcinoma measuring 2 cm. Immunohistochemical analysis (HercepTest) showed HER2 overexpression (3+ in 100% of the cells). Her mother was suffering from hereditary hemochromatosis, and she was heterozygote for point mutation C282Y of the HFE gene.

She started adjuvant chemotherapy with 5-fluorouracil, doxorubicin and cyclophosphamide (FAC) every 3 weeks. At this moment, liver function tests, serum ferritin and transferrin saturation were within normal values. After the fourth cycle, she developed grade 1 serum elevation of transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], that was grade 3 after the fifth cycle. When transaminase levels returned to grade 1, the sixth cycle was administered. One month after the last FAC, she started 3-weekly adjuvant trastuzumab with a loading dose of 8 mg/kg. At this moment, she had adequate liver function tests with only grade 1 ALT [2.3 × under normal limit (UNL)] and ALT (1.7 × UNL) toxic effects. Before the second dose of trastuzumab, grade 4 ALT (1403 U/l, 29.8 × UNL) and grade 3 AST (752 U/l, 16 × UNL) toxic effects were documented. She denied the use of neither illegal drugs nor medicaments, and viral serologies for hepatitis A, B and C, cytomegalovirus and Epstein–Barr virus were negative. Liver ultrasound with Doppler was rigorously normal. Liver enzymes were monitored, and transaminase values got down to grade 1 limits in 4 weeks. Trastuzumab was then reintroduced, at 2 mg/kg every week, and she completed 1 year of treatment with sporadic mild transaminase elevation, with greatest values of ALT and AST of 84 and 53 U/l, respectively (Figure 1).

Trastuzumab is generally well tolerated. Infusion-related reactions, mainly in the first infusion, and reversible cardiotoxicity are the most frequent adverse events. To date, liver toxicity has not been described in relation with trastuzumab therapy [3–6]. Our patient had no history of liver disease, except for HFE gene heterozygosis, which is a frequent condition in European population, and other causes of liver dysfunction, including viral serologies, hepatotoxic drugs and iron overload were ruled out. Accordingly, with the onset and recovery of transaminase levels (Figure 1), trastuzumab seemed the most plausible cause of the acute hepatitis. Although the exact mechanism of injury is unclear, prior liver damage of cyclophosphamide or doxorubicin could play a role in the trastuzumab-induced cytolysis. It may explain in part the absence of recurrence after the reintroduction of trastuzumab 2 months after the last FAC, though a dose-dependent toxicity cannot be excluded.

We want to call attention to this uncommon toxicity because of the expanding role of trastuzumab for the treatment of breast cancer. This should alert physicians to the use of trastuzumab in patients with previous history of liver disease or chemotherapy-induced hepatic toxicity.

Department of Medical Oncology, Hospital de Cruces, Osakidetza-SVS, Plaza de Cruces s/n., 48903 Bizkaia, Basque Country, Spain
(*E-mail: alberto.munozllarena@osakidetza.net

references

doi:10.1093/annonc/mdm515