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LETTER TO THE EDITOR

Death due to liver failure during endocrine therapy for premenopausal breast cancer

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To the Editor,

Acute liver failure is a rare disease occurring in about 2 000 people per year in the USA and 400 per year in the UK. It has been estimated to represent 0.1% of all deaths and 6% of liver deaths [1], but because of its rarity, little is known about etiology and epidemiology. No data are available regarding the incidence of liver failure in premenopausal women undergoing adjuvant endocrine treatment for early breast cancer.

Viral hepatitis A is considered the most common cause of liver failure in tropical countries while in developed countries viral hepatitis B is now a less frequent cause. A recent multicenter prospective study conducted at 17 tertiary care centers in the USA has identified the most common causes of acute liver failure to be acetaminophen (paracetamol) overdosing (39% of cases) and idiosyncratic drug reactions (IDR) (13% of cases) [2]. Among 308 patients with acute liver failure, 73% were women, with a median age of 38 years. Causes of acute liver failure specific to women (such as breast cancer or fatty liver of pregnancy) were only involved in a small number of the cases investigated. It therefore remains to be determined whether women are inherently more susceptible to liver failure, or are at greater risk because of misuse of hepatotoxic medications or other substances (e.g. alcohol).

The role of host polymorphisms in drug metabolism, transportation, regeneration, and immunological pathways in patients with IDR has recently been investigated [3]. Genetic polymorphisms in several key genes or pathways, along with other host and environmental factors, are hypothesized to increase susceptibility to IDR or influence its severity. Moreover, studies of cytochrome P-450 gene polymorphisms in small cohorts of IDR patients have been reported and the development of multiplex platforms may provide further insights [4].

The well-known classically-described drugs with potential hepatotoxicity include acetaminophen, anti-tuberculosis agents, anesthetic drugs of the halothane family, and non-steroidal anti-inflammatory drugs (NSAIDS). Recently, a number of additional IDRs leading to acute liver failure were reported. These reports concern a broad spectrum of antibacterial and antiviral agents, antidepressants, biological agents, and antineoplastic drugs, many of which have only recently been introduced [5–7].

Premenopausal women undergoing endocrine treatment for early breast cancer belong to the age group at risk for use of medications or other agents that cause liver damage. There is little known about hepatic adverse reactions of aromatase inhibitors in this population, but according to recently-published post-marketing surveillance, hepatitis, including cholestatic hepatitis, has been observed with exemestane in postmenopausal women (Aromasin®US prescribing information, revised October 2008).

SOFT/IBCSG 24-02 (Suppression of Ovarian Function Trial) and TEXT/IBCSG25-02 (Tamoxifen vs. Exemestane Trial) are international, multicenter complementary clinical trials coordinated by the International Breast Cancer Study Group (IBCSG) (www.ibcsg.org). Both studies are evaluating the efficacy and safety of tamoxifen versus exemestane in combination with ovarian function suppression (OFS) in premenopausal women with endocrine-responsive early breast cancer. In most patients the GnRH analog triptorelin is used to induce OFS. It is injected intramuscularly once a month. Some patients, by choice, undergo bilateral

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salpingo-oophorectomy or ovarian radiotherapy rather than taking triptorelin.

Since the start of the trials in August 2003, among approximately 4 500 patients randomized, two patients have experienced acute liver failure resulting in deaths without prior cancer recurrence, one while on the SOFT trial, and the other on the TEXT trial.

Patient 1

A 50-year-old patient enrolled in SOFT received triptorelin and exemestane from July 2006 to May 2008. She had a history of alcoholism that resulted in alcoholic fatty liver, acute alcoholic hepatitis, and alcoholic cirrhosis, (liver function tests were normal at randomization) and suffered from depression extensively treated with antidepressants (citalopram, trazodone, mirtazapine). In May 2008 she was admitted to the hospital because of severe liver dysfunction (total bilirubin 23.2 mg/dl, AST 294 mU/ml, ALT 182 mU/ml, GGT 2623 mU/ml, ALP 382 mU/ml). The clinical condition worsened and the patient died in June 2008, with alcoholic hepatitis as the supposed cause of death. Even though it was not possible to obtain details about the patient's alcohol consumption habits, the development of symptoms and changes in liver function tests observed in the 2-year period while she was treated on the SOFT trial were compatible with the diagnosis of progressive alcoholic hepatitis. In this context, a causal relationship between exemestane and the hepatic failure was assessed as unlikely. However, taking into account that the safety of exemestane has not been established in patients with severe hepatic impairment, that exemestane is extensively metabolized by CYP 3A4, and that grade 3–4 elevations of bilirubin, alkaline phosphatase and gamma glutamyl transferase have been documented with exemestane, an additive effect cannot be ruled out.

Patient 2

A 36-year-old patient enrolled in TEXT was treated with GnRH analog from January 2005 to October 2005 (triptorelin for six months and goserelin for three months) before undergoing oophorectomy in November 2005 to eliminate monthly injections per the patient's request. Following completion of chemotherapy she took tamoxifen from August 2005 to June 2006. In June 2006, the patient came to the hospital emergency room after three days of nausea, vomiting, and loose stools. Laboratory and clinical examinations revealed hyponatremia, hypokalemia, abnormal liver enzymes and function, and hepatomegaly. A CT scan showed severe diffuse fatty liver infiltration. Viral hepatitis was ruled out. Tamoxifen was permanently discontinued. She recovered and was discharged after four days. One month later the patient died at home. The initial diagnosis of fatty liver infiltration by CT was attributed to tamoxifen, and there was no evidence for a causal relationship with GnRH analog. According to the autopsy report, the immediate cause of death was intoxication with diphenhydramine. Findings of liver cirrhosis (macrovesicular steatosis, bridging fibrosis) in the course of the autopsy may indicate chronic use of analgesics (not documented but often not reported), which even at therapeutic doses can result in hepatotoxic effects, with the concomitant tamoxifen potentially exacerbating the liver dysfunction.

The three agents prescribed in the SOFT and TEXT clinical trials, triptorelin, exemestane, and tamoxifen, were all considered for possible causal relationships to these deaths in two premenopausal patients with early breast cancer. Both patients received triptorelin, which is eliminated by the kidneys (approximately 42% of the dose) and the liver. In patients with liver dysfunction, renal excretion increases to 62%. Triptorelin clearance decreases and plasma half-life increases in patients with hepatic or renal impairment. Since no metabolites have been identified so far, it seems unlikely that CYP 450 enzymes are involved. According to the product information for triptorelin (Triptorelin Decapetyl®Retard Swiss product information, April 2008), rare cases of transitory, moderate increases of liver enzymes have been reported, but no cases of acute liver failure.

Exemestane is extensively metabolized by CYP 3A4, and similar cumulative amounts of radiolabeled exemestane in urine and feces can be found by pharmacokinetic assay. According to a case report [8] and the current package insert, elevations in bilirubin, alkaline phosphatase, and creatinine were more frequent in patients treated with exemestane than in those treated with tamoxifen (Common Toxicity Criteria grade 3–4 bilirubin elevations in 0.9% patients receiving exemestane vs. 0.1% receiving tamoxifen) (Aromasin®US prescribing information, revised October 2008). For the other aromatase inhibitors (anastrozole, letrozole) increases in liver enzymes (ALP, ALT, AST, and GGT), bilirubin and hepatitis are known characteristics of the adverse event profile listed in the respective prescribing information (www.femara.com, www.arimidex.net).

Tamoxifen is metabolized primarily by CYP 3A4 and 2D6 and is eliminated via feces. In the tamoxifen product information, liver-related side effects are listed and it is recommended to perform periodic liver function tests, although in clinical practice blood tests are no longer performed routinely during follow-up for women with early breast cancer.

The case report forms for Patient 1 indicated concomitant use of antidepressants, which are often metabolized through the CYP 3A4, 2D6, and 2C19 and eliminated mainly or partially by the liver. Elevated liver enzymes and liver failure have been reported during treatment with such drugs alone or in combination with alcohol abuse.

Multiple factors in both of these patients, predominantly drug and alcohol abuse, most likely account for the patients' liver failures and deaths, but we cannot rule out whether tamoxifen or exemestane contributed to worsening the already impaired liver function. Although more difficult to assess, we consider a contribution from triptorelin use highly unlikely.

Young women, in particular between ages 26 to 35, seem to be—for yet unknown reasons—more frequently affected by acute liver failure, and the use of antidepressants (metabolized primarily via liver enzymes CYP 3A4, 2D6, 2C19), other potentially hepatotoxic drugs (e.g. acetaminophen-type analgesics and NSAIDs), and alcohol are more frequent in younger breast cancer patients than generally presumed and reported. We therefore advise physicians to pay special attention to patients treated with endocrine therapy for breast cancer who have concurrent depression and who potentially or actively consume hepatotoxic drugs and alcohol. Such patients should have their liver function monitored and liver imaging should be performed if indicated.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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