Flutamide-associated acute liver failure
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The nonsteroidal antiandrogenic drug flutamide [4'-nitro-3'-(trifluoromethyl)isobutyraniild] is a safe and generally well-tolerated drug used for the treatment of prostate cancer. We describe the case of a 74-year-old male who developed life-threatening acute liver failure during flutamide therapy. Other causes of acute liver failure were appropriately ruled out and there was no evidence of active prostate cancer or liver metastases. The use of the Naranjo probability scale indicated a highly probable relationship between the development of acute liver failure and flutamide therapy. Severe liver dysfunction has been rarely documented in patients treated with flutamide, even though cases of fulminant liver failure have been described. A few cases have been reported also among patients with hirsutism being treated with flutamide. The mechanisms responsible for the occurrence of hepatotoxicity during treatment with flutamide are unknown. Mitochondrial dysfunction seems to be implicated. The potential of flutamide to act as a potent hepatotoxin should be borne in mind when treatment with this drug is being planned.

Key words: Acute liver failure; Flutamide; Hepatitis.

Introduction
The nonsteroidal antiandrogenic drug flutamide [4'-nitro-3'-(trifluoromethyl)isobutyranilide] is a safe and generally well-tolerated drug when used either as a single agent or in combination with a luteinizing hormone-releasing hormone (LHRH)-analogue for the treatment of patients with prostate cancer1-2. We describe the case of a patient who developed life-threatening acute liver failure during flutamide therapy.

Case report
A 74-year-old male was diagnosed as having prostate cancer in July 2002 and treatment with the LHRH-analogue goserelin acetate (3.6 mg every 28 days) and oral flutamide (250 mg thrice daily) was started in August 2002. The results of baseline liver function tests were normal. The serum level of prostate specific antigen (PSA) was 8.4 ng/mL (normal values < 0.4 ng/mL) and the Gleason score was 6.

Early in October 2002 the patient was admitted with a history of progressive fatigue and jaundice, pruritus, anorexia, abdominal pain, dark urine, and pale stool lasting approximately 4 weeks. His past medical history was remarkable for a right nephrectomy because of cancer 20 years previously. The patient did not drink alcohol, to his knowledge he had not been exposed to other hepatotoxins or herbal medicines nor had he received any blood transfusion, and had no other risk factors for exposure to hepatitis or other parenterally transmitted viruses. There was no family history of liver disease and, during the last year before presentation, the patient had not taken any other drugs or over-the-counter medications, except for goserelin acetate and flutamide. He had no history of allergy to any medication and had not recently traveled outside Italy. Furthermore, he reported a weight gain of 4.5 kg (10 lb) over the previous 2 weeks. We interrupted treatment with flutamide and goserelin. At this time, the patient had received only 3.6 mg of goserelin.

On physical examination the patient was fully alert and oriented, afebrile, with intense cutaneous and scleral jaundice, and had no cutaneous stigmata of chronic liver diseases. Vital parameters were normal and heart and chest evaluation was also normal; the neck was supple with flat jugular veins. The abdomen was soft and diffusely tender, with no rebound tenderness and no evidence of organomegaly. However, ascites was present. There was no flapping tremor. Laboratory results included a serum aspartate aminotransferase (AST) concentration of 1707 U/L (normal range 10-36 U/L), an alanine aminotransferase (ALT) concentration of 2372 U/L (normal range 6-40 U/L), an alkaline phosphatase concentration of 820 U/L (normal range 91-258 U/L), and a γ-glutamyltranspeptidase (γ-GT) concentration of 635 U/L (normal range 7-49 U/L). The total and conjugated bilirubin concentrations were 26 and 12 mg/dL respectively, the international normalized ratio (INR) 2.3, the serum fibrinogen concentration 144 mg/dL (normal range 200-400 mg/dL) and the albumin concentration 2.2 g/L. The blood ammonia concentration was 70 μg/L (normal values < 30 μg/L) and that...
of PSA < 0.4 ng/mL (normal values < 0.4 ng/mL). The white blood cell count with differential was normal, and the Westergreen erythrocyte sedimentation rate was 45 mm/hour. The remaining biochemistry and hematology tests were normal. Nucleic acids of the hepatitis B and C viruses, Cytomegalovirus, and Epstein Barr virus were not detected in the peripheral blood. There was no serological evidence of antibodies to the hepatitis A, B, and C viruses, herpes simplex type 1 and 2 viruses, Epstein Barr virus, and Cytomegalovirus, and of the hepatitis B surface antigen. The serum levels of copper, ceruloplasmin and α1-antitrypsin were in the normal range. There was no serological evidence of the presence of autoantibodies.

An ultrasonography and a computed tomographic scan of the abdomen showed an enlarged and bright liver, consistent with a fatty liver, and disclosed the presence of abundant peri-hepatic and perisplenic ascites with no evidence of intra or extrahepatic biliary obstruction or any other abnormality. There was no caval or portal thrombosis. An echocardiography was also normal with no evidence of valvular disease, pericardial effusion, pulmonary hypertension, or left ventricular systolic or diastolic dysfunction.

The patient was started on a therapeutic regimen including paromomycin, lactulose, furosemide, spironolactone, branched amino acids and glucose solutions. During the following 4 weeks his clinical parameters remained stable and at no time were flapping tremor or other signs or symptoms of hepatic failure or encephalopathy observed. However, we documented no change in the liver enzyme levels or in the blood ammonia and bilirubin concentrations until day 36 of his hospital stay when the liver enzymes and bilirubin started to gradually decline. The patient was discharged on day 42 with instructions for close follow-up as an outpatient. At that time, the AST concentration was 375 U/L, ALT 485 U/L, γ-GT 249 U/L, and alkaline phosphatase 91 U/L. The total and conjugated bilirubin levels were 13 and 6 mg/dL, respectively. Three weeks after discharge, the patient still felt fatigued with laboratory studies showing mildly elevated serum concentrations of liver enzymes and bilirubin. His symptoms gradually resolved and serum liver enzyme and bilirubin levels continued to decline over the subsequent follow-up period. The patient did not consent to a liver biopsy and a re-challenge test was not done. At a follow-up visit in February 2003, the patient was doing well but repeat abdominal ultrasonography showed a marked shrinkage of the liver and the persistence of ascites; no other abnormality was seen. At that time, the AST concentration was 112 U/L, ALT 91 U/L, γ-GT 88 U/L, alkaline phosphatase 275 U/L and the total and conjugated bilirubin levels were 10.2 and 3.8 mg/dL, respectively. The INR was 1.4 and the PSA levels were < 0.4 ng/mL. The patient again refused liver biopsy and, when last seen in September 2003, he was asymptomatic with normal blood levels of bilirubin and liver enzymes. The PSA levels were < 0.4 ng/mL and the patient had no evidence of active prostate cancer.

**Discussion**

The use of the Naranjo probability scale for adverse drug reactions indicated a highly probable relationship between the development of acute liver failure and flutamide therapy. Other causes of acute liver failure were appropriately ruled out and the patient had no evidence of active prostate cancer or liver metastases. There was no reason to suspect goserelin as the culprit in this case. The patient indeed received only 3.6 mg of goserelin 5 weeks before presentation and, in our opinion, the lack of a clear temporal relationship with the onset of acute liver failure renders any hypothesis in favor of a causal role of goserelin highly unlikely. Furthermore, to the best of our knowledge, there is no report of patients in whom treatment with goserelin acetate or any other LHRH-analogue was implicated as a potential cause of hepatitis or acute liver failure.

Owing to its efficacy, convenient oral dosing, and favorable profile of safety and tolerability, flutamide is a widely accepted agent for the treatment of patients with advanced prostate cancer. Toxic effects of flutamide, in particular gynecomastia and diarhea, have been rarely reported and in most cases they were mild and self-limited with immediate recovery achieved after lowering doses or temporarily interrupting treatment. In a review of the literature we found a few other cases of flutamide-induced acute hepatitis and, among them, even patients with fulminant liver failure and patients who had a fatal outcome. Liver toxicity is thought to be a very rare event that occurs in about 3 per 10 000 expositions among patients with advanced prostate cancer treated with flutamide and in most instances only a transient and self-limited increase in serum liver enzymes has been documented. The potential risk of inducing severe hepatitis with flutamide should be borne in mind even if the drug is used in clinical settings other than the treatment of advanced prostate cancer. At least 3 cases of fulminant liver failure have been indeed described among women who were given flutamide for the treatment of hirsutism.

Hepatitis and acute liver failure are toxic effects of flutamide the mechanism of which is still incompletely known. Flutamide is rapidly converted mainly by cytochrome P450 (CYP1A2) to its active metabolite, 2-hydroxyflutamide, by first-pass metabolism with subsequent hydrolysis to 3-trifluoromethyl-4-nitroaniline, or...
La flutamide [4′-nitro-3′-(trifluoromethyl)isobutyramidide] è un antiandrogeno non steroideo generalmente considerato sicuro e ben tollerato quando utilizzato da solo o in combinazione con un analogo dell’ormone luteinizzante nel trattamento dell’irsutismo. I meccanismi molecolari responsabili della tossicità epatica da flutamide non sono conosciuti. Sembra essere implicata un’alterata funzione mitocondriale. La possibilità di un’epatotossicità grave deve essere considerata quando si decide di iniziare un trattamento a base di flutamide.

Parole chiave: Epatite; Flutamide; Insufficienza epatica grave.

References


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