Toxic hepatitis secondary to oral administration of exemestane

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Hepatitis tóxica secundaria a la administración oral de exemestano: caso clínico

Los inhibidores de aromatasa se prescriben a pacientes con cáncer de mama que han progresado tras la administración de tamoxifeno. Los efectos adversos son mínimos o moderados y de fácil manejo.
De acuerdo con lo publicado hasta la fecha, ésta es la primera descripción de un caso de hepatitis tóxica secundaria al uso de exemestano.
Describimos el caso de una paciente de 65 años con cáncer de mama estadio IV con metástasis óseas que recibió exemestano como segunda línea de hormonoterapia. Después de dos meses de tomarlo de forma continua, la paciente inició cuadro de ictericia progresiva con serología vírica negativa y elevación de las enzimas hepáticas. El diagnóstico de hepatitis tóxica se llevó a cabo mediante exploración física y hallazgos analíticos. La resolución del cuadro se produjo tras la retirada del medicamento, observándose mejoría progresiva de su estado general y normalización de los parámetros analíticos.

Palabras clave: reacción adversa, hepatitis tóxica, hormonoterapia, exemestano.

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INTRODUCTION

Exemestane is an irreversible steroid aromatase inactivator that is given, alone or in combination with chemotherapeutic agents, to patients with stage IV breast cancer. Adverse reactions are uncommon and toxic hepatitis has not been reported to occur with its use[1,2].
We describe a case with this type of toxicity related with the oral use of exemestane (Pharmacia & Upjohn).

CASE REPORT

A 65 year-old healthy woman, with no personal history of diseases, alergies or use of any medication, was referred to our hospital and was diagnosed in March 2000 as having locally advanced cancer of the right breast. Complete response was achieved with 6 cycles of poly-chemotherapy and radiotherapy. Thenafter, tamoxifene was taken by the patient during 6 months without any secondary effect. No concurrent or complementary medication was used and the blood test were rigorously normal (hemogram and routine chemistry). Six months later, the patient did not show any disconfort but silent bone metastases were noted in a oseous gamagraphy and in a pelvic x-ray. A second line of hormone therapy with exemestane (25 mg, oral, once daily) was initiated. Routine blood tests, including hemogram, hepatic enzymes, lipids, electrolytes and coagulation, were normal.
Two months later the patient's skin and conjunctiva appeared jaundiced and she complained of general itchiness. There was no hepatomegaly. Blood analysis showed: white blood cells: 12.0 $x10^3$/ml; haemoglobin: 14.2 g/dl; platelets: 259 $x10^3$/ml; total bilirubin: 13.83 mg/dl (reference range RR = 0 - 1.1); conjugated bilirubin: 11.25 mg/dl (RR = 0 - 0.25); lactate dehydrogenase: 665 U/l (RR = 23 - 198); alanine aminotransferase: 69 U/l (RR = 1 - 40); aspartate aminotransferase: 45 U/l (RR = 1 - 37); gamma-glutamyltranferase: 94 U/l (RR = 7 - 40); alkaline phosphatase: 690 U/l (RR = 98 - 240); cholesterol: 302 mg/dl (RR = 120 - 220); HDL cholesterol: 9 mg/dl (RR = 35 - 80); triglycerides: 390 mg/dl (RR = 35 - 300); apo B: 215 mg/dl (RR = 60 - 117); total protein: 6.3 g/dl (RR = 6.5 - 8.3); carcinoembriyogenic antigen: 109 ng/ml (RR = 0 - 5); IgG 830 mg/dl (RR = 700 - 1600); IgM 82.9 mg/dl (RR = 40 - 230); IgA 95.3 mg/dl (RR = 70 - 400); alfa feto protein 1.59 ng/ml (RR = 0 - 10); carbohydrate antigen 19-9: 5.34 U/ml

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(RR = 0 - 37); carbohydrate antigen 15,3: 29.1 U/ml (RR = 0 - 40); T4: 1.41 ng/dl (RR = 0.71 - 1.9); TSH 3.01 uUl/ml (RR = 0.35 - 5). All of the following tests were negative: anti-IgM hepatitis A virus by EIA; detection of RNA-VCR by PCR; HBsAb by EIA; HB virus anti-core by EIA; anti-IgG hepatitis C virus by EIA; antinuclear Ab (IFI) and (EIA); anti-DNA Ab (IFI); anti-smooth muscle Ab; anti-parietal cells Ab; antimitochondrial Ab; EBV and HIV.

The abdominal echography and hepatic CT scan were normal. Fine needle biopsy of the liver was not performed.

The medication was discontinued, anti-histamines were prescribed and glutation at recommended doses was administered over four weeks.

Patient recovery was monitored every week until normalisation of the blood analyses occurred at around 4 months. To-date, she is in relatively good health and not in receipt of any medication.

DISCUSSION

Exemestane is a new steroidal aromatase inactivator that has been shown to have considerable activity in the treatment of postmenopausal women with hormonal sensitive breast cancer. The drug, administered orally at a dosage of 25 mg once daily, was shown to suppress aromatase activity by 97.9% *in vivo* with a subsequent reduction >85% of circulating oestrogen levels. It exhibits definite anti-tumour activity at a relatively low daily dosage, and is highly potent, highly selective, and well tolerated.

Moreover, for postmenopausal women with metastatic breast cancer, exemestane demonstrated a higher activity and better toxicity profile when compared to megestrol acetate and tamoxifen in second- and first-line therapy, respectively[3].

Severe (grade 3-4) adverse toxic events related to exemestane use are infrequent. In a Phase III randomised trial with 769 patients, 366 of whom were in the exemestane treatment group, there were 284 (79.3%) different kinds and grades of toxicities (grades 1-4) observed. The most frequent adverse reactions were low-grade hot flushes (12.6%), nausea (9.2%), fatigue (7.5%) and weight changes. In this study non elevated values of hepatic enzimes were observed[4].

There has been described some grade 3-4 hepatic enzimes or alcaline phosphastase but only related with hepatic damage, bone or liver metastases[5]. Similar findings have been reported by other authors[6-9].

To the best of our knowledge there has not been any case of toxic hepatitis reported in association with this drug's use. Exemestane may be a rare cause of toxic hepatitis but, being a relatively new drug, this report could serve as a caution for those oncologists who are contemplating its regular use in women with refractory breast cancer.

Key words: adverse reaction, toxic hepatitis, hormone therapy, exemestane.

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