Eur J Cancer Clin Oncol, Vol. 22, No. 9, pp. 1121–1122, 1986.
Printed in Great Britain

0277-5379/86$3.00+0.00
Pergamon Journals Ltd.

Letter to the Editor

Hepatocellular Damage by Cyproterone Acetate

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RECENTLY there has been a growing interest in the use of progestational drugs in the treatment of patients with advanced breast cancer. Promising results have been found with medroxyprogesterone acetate in higher dosage [1]. Another drug with strong progestative effects is cyproterone acetate (CPA). This drug normally is used as an anti-androgen for the treatment of hirsutism or acne in female [2],and for prostatic cancer in male patients. CPA is usually tolerated very well, and no major adverse or side-effects have been reported so far [3].

In a phase II study 20 postmenopausal patients with advanced breast cancer were treated with CPA in a dosage of 200–400 mg daily, for a period of 6–52 (mean 24) weeks. Three patients developed transaminase activity, which was up to three times normal (WHO toxicity grade I). Liver metastases were absent on ultrasound examination. Two patients developed liver function tests up to 10 times normal (WHO grade IV), with slightly elevated bilirubin levels (WHO grade I toxicity). Liver metastases and viral hepatitis were excluded by a liver scan and virus serology in both patients. Neither had used other medication. A liver biopsy in the first patient, 73 yr old, after 11 weeks on 400 mg CPA, showed acute diffuse hepatitis with confluent and bridging necrosis, irregular scarring and evidence of regeneration. No cirrhosis, granuloma formation or cholestasis was present. Liver functions normalized 4–9 weeks after CPA was terminated (Fig. 1).

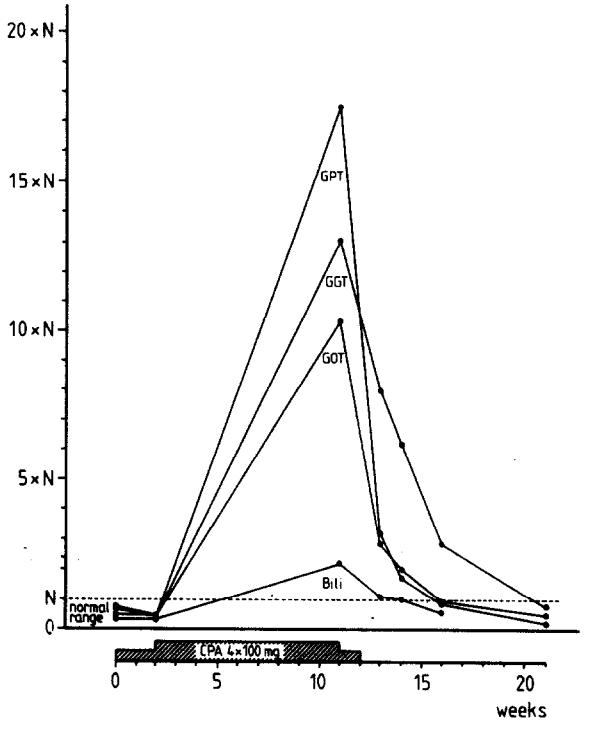

Fig. 1. Results of the liver function tests of the first patient. CPA was given at a dose of 400 mg *daily, except for the first 2* weeks *and the last week (at* 200 mg*) daily. N = upper limit of normal range, comparatively for each parameter (Alk. phosph. remained less than* 2 × *N).*

Liver biopsy in the second patient, 85 yr old, was done after 21 weeks on 200 mg CPA daily. Similar to the first patient, acute hepatitis with bridging necrosis, regeneration of liver tissue and beginning post-hepatitis scarring were observed. Her symptoms clearly improved after termination of CPA treatment, but liver function tests normalized only 3 months thereafter.

Accepted 20 March 1986.
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In this study, 5 out of 20 patients showed liver function disturbances during CPA therapy, that could not be attributed to liver metastases nor to viral hepatitis, nor to the use of any concomitant medication. Measurement of the indicator lesions did not demonstrate a 'flare up' caused by CPA treatment, as had been described incidentally for related compounds [4, 5].

We could not find any data in the literature over the past 15 yr on clinical hepatotoxicity of CPA. Although in a chronic toxicity study the development of hepatomas and elevated liver functions have been found in rats [6], no evidence of liver damage in man has been reported during long term use of CPA in these dosages [2, 7, 8, 9].

In contrast to the numerous reports on cholestatic jaundice caused by synthetic steriods, only a few authors mention hepatocellular damage, with histological signs of inflammation and necrosis, as a result of therapy with these compounds. In a review on drug-induced liver damage, oral contraceptives are mentioned [9] and we found just one report on severe hepatitis following the use of the progestin norethindrone [10].

The two patients described here both suffered from serious hepatocellular damage. Liver biopsies in both showed hepatitis with bridging and confluent necrosis and evidence of beginning post-hepatitic scarring which in the long run might lead to cirrhosis.

The precise cause of this unusual toxicity pattern remains uncertain but the advanced age of both our patients may be a factor to consider [11].

We think the present observations may be of interest because the use of CPA is gaining wider acceptance for the treatment of patients with prostatic cancer, which mostly concerns an elderly population as well. Disturbed liver function in these patients may falsely suggest the presence of metastatic liver disease and thus lead to inappropriate therapeutic decisions. Fortunately, in our patients the termination of CPA resulted in complete recovery in both patients, without further therapeutic interventions.

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