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Letter

Exemestane seems to stimulate tumour growth in men with prostate carcinoma

Advanced prostate cancer is responsive to first line androgen manipulation with regressions being observed in up to 80% of treated patients [1,2]. After progression, in spite of significant androgen blockade, anti-androgen withdrawal may still induce tumour regression in some and clinical benefit in many [3–5]. Ketoconazole, an antimycotic agent with some anti-aromatase properties, was shown to be effective in patients with progressive prostate cancer on anti-androgen treatment and their subsequent withdrawal [6]. *In-vitro* observations have resulted in the hypothesis that testosterone might still be indirectly effective in stimulating androgen-unresponsive prostate cancer cells through its *in-situ* conversion into oestrogen in a reaction catalysed by aromatase [7–10]. Patients treated with 4-hydroxyandrostenedione, a steroidal aromatase inhibitor, showed some subjective responses through pain relief and an increased performance status, but there were no objective tumour regressions [11]. Some patients experienced a transient 'tumour flare', represented by an increase in bone pain soon after commencing treatment [12]. A clinical study with anastrozole, a second-generation aromatase inhibitor, showed only a minimal improvement in bone pain, without any objective responses being observed [13]. We therefore started a randomised phase II trial with exemestane, an orally active, steroidal, irreversible aromatase inactivator with weak androgen effects, given either with or without bicalutamide, as second-line therapy. Patients continued first-line androgen suppression (lutenising-hormone-releasing hormone (LHRH)-agonist or orchiectomy). Bicalutamide was randomly added to investigate the potential antagonistic effect of the weak androgen action of exemestane.

5 patients were randomised, of whom 4 were treated with exemestane (2 with, 2 without bicalutamide). Progression (prostate-specific antigen (PSA), radiological signs) was documented after 4 weeks. 3 out of 4 patients showed a significant increase in bone pain only a few days after starting treatment and a clear improvement in these symptoms after its cessation. 3 patients had a clear PSA progression and a stabilisation or regression of the PSA value after stopping the trial treatment. 2 patients had a radiological progression during therapy; 1 with a pathological lumbar bone fracture, 1 with an increase in the number of lung metastases. One patient became anaemic during the treatment. The concentration of testosterone was determined in 2 patients who had undergone a surgical castration following progression under the trial treatment (both had received bicalutamide). A relative increase in this low, postcastration value could be observed, in parallel with an augmentation of the PSA value. After stopping the trial treatment, both values regressed.

In conclusion, the observation of an immediate clinical deterioration and the hint for improvement upon withdrawal of exemestane caused the early cessation of the trial. The relative increase in the testosterone concentration observed during the trial treatment should motivate further research into endocrine-responsive diseases. Exemestane seems to have no role to play in the treatment of prostate cancer.

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