Experience with fulvestrant acetate in castration-resistant prostate cancer patients

introduction

Fulvestrant is a selective estrogen receptor (ER) down-regulator; fulvestrant inhibits ER dimerization [1] and reduces ER’s half-life [2]. In preclinical models, fulvestrant inhibited cell growth of the DU145 prostate cancer (PCa) cell line through an ER-β-dependent mechanism [3]. Metastatic PCa expresses ER-β mainly in metastases to the lymph nodes and bones [4]. Androgen receptor (AR) expression is retained in a significant proportion of castration-resistant prostate cancer (CRPC) [5]. Bhattacharyya treated PCa cell lines with fulvestrant obtaining a 70% of inhibition of the cell growth, demonstrating that fulvestrant is a potent AR down-regulator [6]; thus, combined down-regulation of ARs and ERs appears as an attractive strategy for treating CRPC.

materials and methods

From June 2008 to January 2009, seven performance status (PS) of zero to two on the ECOG scale (PS 0, one patient; PS 2, four patients; PS 2, two patients) CRPC patients, evidenced by a progressively rising prostate-specific antigen (PSA) or an increase in tumor mass on bone scan, X-ray, computed tomography scan or magnetic resonance imaging despite a castrate level of testosterone (testosterone <20 ng/dl) when they received the first line of chemotherapy, were treated with 500 mg of fulvestrant i.m. every 14 days for the first month and 250 mg monthly thereafter. Neither the number of previous hormonal therapies nor the number of chemotherapy treatments was limited. Patients had a mean age of 74 years (range 54–83 years). All patients had received two to four lines of prior hormone therapy (mean 3.14). Five patients had received at least one chemotherapy line; the number of chemotherapy lines varied from 1 to 3 (mean 1.80). One patient had received oral sunitinib. All patients had detectable PSA levels at the start of fulvestrant.
The patients presented with a median baseline PSA of 189 ng/ml (range 21.9–2462 ng/ml) before the first treatment.

results
A total of 55 injections of fulvestrant were administered. The mean number of administrations was 7.83 (7–9). Grade 2 asthenia in one patient was the only recorded side-effect in our cohort.

In six of the seven treated patients, a PSA level reduction was recorded. The maximum PSA decrease observed ranged from 40% to 99% (median 60%). PSA response was established in five of these six patients. The median observed duration of PSA response was 1.50 months (range 0.27–2.67 months) (Figure 1).

One patient refused treatment continuation despite PSA control and was lost to follow-up.

discussion
The role of additional hormonal manipulations in CRPC patients progressing on cytotoxic chemotherapy has not been well defined. Recently, interesting data have been provided with the use of abiraterone acetate [7], ketoconazole [8], and diethylstilbestrol [9], supporting the hypotheses of the existence of some degree of androgen dependence in the context of CRPC that can be exploited to treat this disease.

In our case, we analyzed the responses to fulvestrant acetate in seven highly pretreated CRPC patients. We observed a mean PSA decrease of 68.3% in patients who responded. No relevant side-effect was recorded.

Our results differ, and compare favorably, with the trial of Chadha et al. [10] where no PSA response was obtained. However, Chadha didn’t use a loading-dose schedule. In our cohort, the PSA began to rise soon after the fulvestrant dose was reduced to monthly 250 mg; so, under our point of view, the existence of a phenomenon of dose response for fulvestrant in Pca should be considered. On the basis of our results, we propose additional investigations of fulvestrant in patients with CRPC as well as the inclusion of fulvestrant in future trials of Pca.

J. M. Gasent Blesa1*, V. Alberola Candel2, V. Giner Marco3, V. Giner-Bosch4, M. Provencio Pulla4 & J. B. Laforga Canales4

1Department of Medical Oncology, Hospital de Dénia, Marina Salud, Dénia, Country of Valencia, 2Department of Medical Oncology, Hospital Arnau de Vilanova, València, 3Department of Medical Oncology, Hospital de Sagunt, Sagunt, 4Department of Applied Statistics, Operations Research and Quality, Universitat Politècnica de València, Valencia, 5Department of Medical Oncology, Hospital Universitario Puerta de Hierro, Madrid, 6Department of Pathology, Hospital de Dénia, Marina Salud, Dénia, Spain (*E-mail: joanmagasent@telefonica.net)

references

doi:10.1093/annonc/mdq010
Published online 5 February 2010