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.

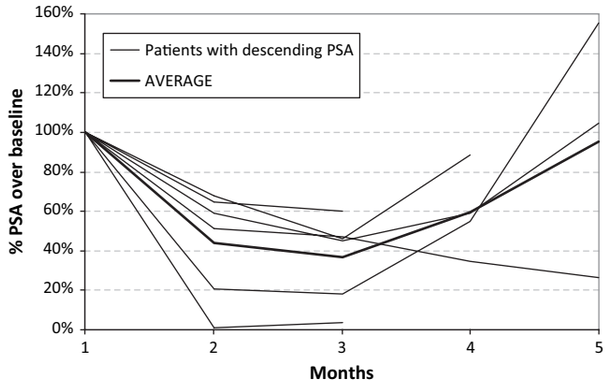

Figure 1. Prostate-specific antigen (PSA) level evolution in the group of responding patients.

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 Blesa[1]*, V. Alberola Candel[2], V. Giner Marco[3], V. Giner-Bosch[4], M. Provencio Pulla[5] & J. B. Laforga Canales[6]

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

references

1. Fawell SE, White R, Hoare S et al. Inhibition of estrogen receptor-DNA binding by the ''pure'' antiestrogen ICI 164,384 appears to be mediated by impaired receptor dimerization. Proc Natl Acad Sci U S A 1990; 87: 6883–6887.
2. Dauvois S, Danielian PS, White R, Parker MG. Antiestrogen ICI 164,384 reduces cellular estrogen receptor content by increasing its turnover. Proc Natl Acad Sci U S A 1992; 89: 4037–4041.
3. Lau KM, LaSpina M, Long J, Ho SM. Expression of estrogen receptor (ER)-alpha and ER-beta in normal and malignant prostatic epithelial cells: regulation by methylation and involvement in growth regulation. Cancer Res 2000; 60: 3175–3182.
4. Leav I, Lau KM, Adams JY et al. Comparative studies of the estrogen receptors beta and alpha and the androgen receptor in normal human prostate glands, dysplasia, and in primary and metastatic carcinoma. Am J Pathol 2001; 159: 79–92.
5. Santos AF, Huang H, Tindall DJ. The androgen receptor: a potential target for therapy of prostate cancer. Steroids 2004; 69: 79–85.
6. Rumi S, Bhattacharyya R, Aruna V et al. Fulvestrant (ICI 182,780) down-regulates androgen receptor expression and diminishes androgenic responses in LNCaP human prostate cancer cells. Mol Cancer Ther 2006; 5: 1539–1549.
7. Danila DC, Rathkopf DE, Morris MJ et al. Abiraterone acetate and prednisone in patients with progressive metastatic castration resistant prostate cancer after failure of docetaxel-based chemotherapy. Proc Am Soc Clin Oncol 2008; 26: (Abstr 5019).
8. Galsky MD, Simon K, Sonpavde G et al. Ketoconazole retains activity in patients with docetaxel-refractory prostate cancer. Ann Oncol 2009; 20: 965–966.
9. Serrate C, Loriot Y, De La Motte Rouge T et al. Diethylstilbestrol (DES) retains activity and is a reasonable option in patients previously treated with docetaxel for castration-resistant prostate cancer. Ann Oncol 2009; 20: 965.
10. Chadha MK, Ashraf U, Lawrence D. Phase II study of fulvestrant (faslodex®) in castration resistant prostate cancer. Prostate 2008; 68: 1461–1466.

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