Do We Really Need New Trials on Fulvestrant in Prostate Cancer?

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J.M. Gasent Blesa and V. Alberola Candel report in this issue of ONKOLOGIE on the case of a metastatic prostate cancer patient successfully treated with fulvestrant [1]. This 79 year-old patient with initially metastatic prostate cancer first received complete androgen blockade (CAB) and then high-dose bicalutamide because of intolerance to LH-RH agonist. One year later the patient had symptomatic disease progression. All androgen deprivation was stopped and the patient received 7 cycles of docetaxel plus prednisone. He had asymptomatic stable disease for a whole year without further treatment, then the disease progressed with symptoms and fulvestrant was administered. After two intramuscular injections of 500 mg fulvestrant at 14 days interval, the patient experienced dramatic pain decrease and significant serum PSA decline. We rejoice at the good result for the patient, but this case report raises two major concerns: the problem of the hormonal status of the disease and the interest of further studies of fulvestrant in this indication.

In this clinical case, the patient did not have castration-refractory prostate cancer (CRPC). As determined by a panel of investigators [2], CRPC requires the continuation of some form of androgen deprivation (orchidectomy or LH-RH agonist) together with castration serum testosterone level and discontinuation of any anti-androgen to avoid possible anti-androgen withdrawal syndrome. Moreover, according to American Society of Clinical Oncology (ASCO) recommendations [3], chemotherapy is only indicated in case of CRPC. The patient discontinued hormonal treatment in February 2007 and received chemotherapy, finally he received fulvestrant in February 2009. The serum testosterone level is not known. Therefore this patient may still have androgen-sensitive disease.

The authors refer to a phase 2 trial on fulvestrant which actually failed to demonstrate any activity of this drug [4]. This study was well designed and well conducted. All 20 eligible patients had true CRPC, and 16 had measurable disease. There were neither objective responses nor a significant serum PSA decline according to current PSA response criteria [5]. Thus, it is very un-

likely that the case report presented here can plead for a new prospective study on fulvestrant in CRPC. It is interesting to shortly review the major approaches for identifying new drugs with potential activity on hormone receptors in CRPC.

The characteristic of CRPC is an overexpression of androgen receptors (AR) associated with different genetic modifications (AR mutation, for instance). One important point is the affinity between the ligand (androgens) and AR, and therefore the transcription mechanisms regulating ligand-dependent proliferation, metastatic capacity, etc. [6]. The concept of complete androgen blockade appeared very early when LH-RH agonists were introduced into clinical practice, together with the first anti-androgens [7]. It has been demonstrated that even healthy men receiving LH-RH agonist therapy have a persistent concentration of androgens in their prostatic tissues [8]. Therefore the major question is the balance between drug affinity and androgen affinity to AR and, in a second step, the transcriptional activity of the intracellular ligand. The ideal drug would thus be a drug with the highest possible affinity to AR (higher than that of androgens) and with transcriptional inhibition activity. There have been only few such candidates, but some new substances have been developed recently: Fulvestrant is an antiestrogen which can suppress AR expression in several models [9]. It acts by directly repressing AR transcription, resulting in decreased tumour growth. Mifepristone is a progesterone antagonist with more potent AR antagonist activity than other anti-androgens. It mediates the recruitment of NCoR and SMRT co-repressors, but has no major clinical activity [10]. VN/124-1 is an AR antagonist, more powerful than bicalutamide, which is potentiated by tyrosine kinase inhibitors (TKI) and is active in different pathways, particularly the mTOR pathway [11]. There are balances between the activities of the different transduction pathways and AR expression. Transduction pathways should probably be considered when testing AR antagonists: their inhibition may restore sensitivity to androgen antagonists. Another therapeutic pathway could be interesting to explore:

serum/glucocorticoid-regulated kinase 1 (SGK1) [12], an androgen-regulated target gene in cellular models of prostate cancer. Its protein, as determined by the phosphorylation of its target, Nedd4-2, increases with androgen treatment. RNA interference-mediated knockdown of SGK1 expression attenuates the androgen-mediated growth of the prostate cancer cell line LNCaP. The small-molecule competitive inhibitor GSK650394 blocks the effect of androgens on LNCaP cell growth. Thus, in addition to androgen ablation, inhibition of such pathways downstream of AR is likely to have therapeutic utility for prostate cancer treatment. Arsenic trioxide seems to induce a deficiency in AR-chromatin binding by disruption of AR amino and carboxyl termini interaction [13]. No clinical trials have yet been published in CRPC patients.

To date, the most promising drugs are abiraterone acetate and MDV3100. Abiraterone acetate [14] is an inhibitor of enzymes involved in the transformation of cholesterol to estrogens and progesterone. It is an inhibitor of 17 α hydroxylase and C 17–20 lyase [15]. Its activity is dependent on binding to AR (competitive with androgens but also with anti-androgens). The drug seems to be safe [14]. The first results published demonstrate some activity in patients with CRPC [16]. MDV3100 is a

small-molecule AR antagonist. It has very high affinity to AR, higher than that of bicalutamide and of natural androgens, and it is a potent inhibitor of AR transcription. A recent phase I/II study included 140 CRPC patients, but only 114 were evaluated for response at a dose of 240 mg/day [17]. Half of them had received prior chemotherapy. Roughly, 40% of patients had measurable disease; 90% had bone disease. Except for the 3 cases of seizure at a dose of 360 mg, overall tolerance was good. Fatigue was the major side effect. Partial response was observed in 16 and 9% of chemo-naïve and chemo-treated patients, respectively. A majority of patients had a favorable evolution of their circulating tumor cell profile [18]. The waterfall plot of post-treatment PSA change at 12 weeks was impressive. It appeared similar in chemo-naïve and chemo-treated patients. The developments in second-generation anti-androgens look very promising [19]. This should lead clinical researchers to concentrate their effort on large randomized trials of these drugs.

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