Case Study of the Month

Durable Complete Response to Frontline Docetaxel in an Advanced Prostate Cancer Patient with Favourable CYP1B1 Isoforms: Suggestion for Changing Paradigms?

Giovanni Brandi,*, Francesco de Rosa, Romano Danesi, Gian Carlo Montini, Guido Biasco

Institute of Haematology and Medical Oncology “L. e A. Seràgnoli”, Policlinico Sant’Orsola Malpighi, University of Bologna, Bologna, Italy

Department of Internal Medicine, University of Pisa, Pisa, Italy

Service of Nuclear Medicine, Policlinico Sant’Orsola Malpighi, Bologna, Italy

1. Case report

In June 2006, we evaluated a 55-yr-old male who had undergone nerve-sparing radical prostatectomy in another institution for prostate cancer. His preoperative prostate-specific antigen (PSA) was 5.7 ng/ml, free PSA 9.2%, and clinical staging T1c. The transrectal biopsy showed prostatic adenocarcinoma (Gleason score 3 + 3) in 7 out of 10 specimens with cancer representing up to 60–70% of each core, perineural neoplastic infiltration, and no strong evidence of vascular and lymphatic invasion. The postoperative histologic examination showed multifocal adenocarcinoma, Gleason score 3 + 4 and 4 + 5 in different lobes, with infiltration of the resection edge but not of the prostatic capsule. Seminal vesicles were not involved by the disease. One lymph node out of 21 examined was metastatic;
therefore, the pathologic stage was pT2c N1 MX. Postoperative PSA level was 0.5 ng/ml, suggesting residual disease. To further evaluate its extension, an $^{11}$C-choline positron-emission tomography/computed tomography (PET/CT) was performed: it showed areas of high tracer uptake in the prostatic lodge (see Fig. 1) and in a lumbar aortic lymph node (see Fig. 2), strongly suggestive of residual disease.

Given the relatively young age of the patient, the high risk of clinical progression, and published data concerning the role of CYP1B1 in docetaxel chemosensitivity [1,2] and its expression in prostate carcinoma [3], we offered him a genetic test to find out which specific isoform of the enzyme he harboured. He was heterozygous for both 1666 C>G (Leu432Val) and 1730 A>G (Asn453Ser) variants. The isoforms Leu432 and Ser453 are characterised by an inferior catalytic activity [4], and even if docetaxel is not metabolised by CYP1B1 [5], its low activity is supposed to favourably influence docetaxel sensitivity due to the impaired production of oestrogen metabolites, which could interfere with binding of the drug to tubulin [6].

Therefore, we proposed treatment with docetaxel, 75 mg/m² every 3 wk for six cycles, followed by radiotherapy. The patient gave his consent, and chemotherapy started in July 2006. In August, after two cycles, an early $^{11}$C-choline PET/CT response evaluation showed the disappearance of the high-uptake areas previously identified (see Figs. 3 and 4). A contrast-enhanced CT scan was also consistent with complete response.

After four other cycles of chemotherapy, the patient was reevaluated: his PSA level was 0.01 ng/ml, indicating complete biochemical response. The therapeutic program continued as planned with external beam radiation therapy, which started in
December 2006. Total doses of 46 Gy, 66 Gy, and 50 Gy were delivered to the pelvis, prostatic lodge, and lumbar aortic lymph nodes, respectively, with conventional fractioning. Treatment was reasonably well tolerated except for mild to moderate nausea, which did not require therapy discontinuation. As maintenance treatment, we started androgen deprivation therapy with leuprorelin, which is planned for at least 2 yr and is still ongoing.

In July 2007, a new disease evaluation by $^{11}$C-choline PET/CT was performed and showed a high metabolic activity area in the left lobe of the liver. The lesion was further investigated with sulphur hexafluoride microbubbles contrast-enhanced ultrasonography, which characterised the finding as an avascular, focal area of steatosis and also identified two other similar lesions. This, together with the still-suppressed PSA level, confirmed the status of complete remission.

The patient is now followed up regularly with PET/CT and serum PSA determination; he has been disease-free since August 2006.

2. Discussion

The current first-line therapy for metastatic prostate cancer is represented by castration, either surgical or pharmacological (long-acting luteinising hormone-releasing hormone [LHRH] antagonists) [7]. Such a strategy, however, cannot achieve cure: median survival ranges between 20 and 40 mo [8]. This can be of concern, especially in younger patients, who are affected by a substantial reduction
in life expectancy. New treatment options are therefore needed.

This case is paradigmatic from many aspects. First, it suggests that chemotherapy may also be effective in earlier stage disease, especially as first-line treatment. Actually, androgen deprivation therapy suppresses the malignant clone but does not have the ability to eradicate it, as cytotoxic drugs do. This may be important, especially in the setting of high-risk disease in younger patients (e.g., high Gleason score or residual disease after radical prostatectomy).

Androgen deprivation therapy may therefore be used as maintenance treatment, as currently happens in other hormone-sensitive malignancies—namely, breast cancer—with significant contribution to the global efficacy of therapeutic protocols. In this context, a recently published retrospective experience [9] also suggests that further investigation of first-line combination of hormonal and cytotoxic therapy in a prospective trial is warranted.

A criterion for rational indication of docetaxel therapy may also be the predicted sensitivity to the drug on the basis of CYP1B1 variants. Our patient had a good early response (PET/CT negative after two docetaxel cycles and PSA 0.01 ng/ml), maybe also because of the absence of unfavourable genotype. Recently, the importance of the polymorphism 1666 C>G has been retrospectively confirmed in vivo and in prostate cancer patients [6], with significant impact on survival.

Eventually, our case suggests that first-line chemotherapy together with radiotherapy may be effective in advanced prostate cancer, especially in patients with favourable CYP1B1 variants. Thus, physicians might offer chemotherapy to people who are likely to benefit and avoid exposing others to its adverse effects, at least in first-line treatment. Prospective trials investigating such a strategy are therefore warranted and are currently planned in our institution.

Conflicts of interest

The authors have nothing to disclose.

Question:

Which cytochrome P450 isofor can influence docetaxel chemosensitivity?

A. CYP3A4
B. CYP2D6
C. CYP1B1
D. CYP2E1

References


EU-ACME question

Please visit www.eu-acme.org/europeanurology to answer the below EU-ACME question on-line (the EU-ACME credits will then be attributed automatically).