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Why castration-resistant prostate cancer patients with neuroendocrine differentiation should be addressed to a cisplatin-based regimen

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In a recent paper, Loriot et al. [1] explored the issue of whether carboplatin plus etoposide regimen is more active in castration-resistant prostate cancer patients with neuroendocrine differentiation as opposed to those without. In a patient population resistant to docetaxel therapy, they observed a prostate-specific antigen (PSA) response rate in 18% and 31% of patients with normal and elevated serum chromogranin A (CgA), respectively. These results indicate a possible role of neuroendocrine differentiation in predicting efficacy of cisplatin-based regimen.

How to explain these data? Platinum-containing regimens are notoriously efficacious in the treatment of pure poorly differentiated neuroendocrine prostate carcinoma that is an extremely rare phenotype [2]. In most cases of prostate cancer with neuroendocrine differentiation, the neuroendocrine cell population coexists with a predominant exocrine phenotype. Noteworthy, these neuroendocrine cells are apparently terminal cells, since they do not proliferate. Conceivably, they could negatively influence the prognosis by stimulating the exocrine component of the tumor to proliferate via paracrine mechanisms [3]. On these bases, there is no rationale supporting a greater sensitivity of prostate cancer with neuroendocrine differentiation to cisplatin-containing regimens.

We report on a case that was recently addressed to our institution. A 69-year-old patient had a castration-resistant prostate carcinoma with multiple bilateral lung metastases and metastatic bone lesions. Radical prostatectomy was carried out in 2002 and an adenocarcinoma, Gleason score 7, stage pT3b pN0 was found. CgA immunoreactivity was detected in 1% of tumor cells. Preoperative serum PSA was 7 ng/ml. Two years later, he had been addressed to androgen deprivation therapy (ADT) due to bone progression and in March 2006, docetaxel therapy was introduced due to lung metastases development. After three chemotherapy cycles, however, a further progression of lung lesions was observed. Serum PSA and plasma CgA were 20.4 ng/ml and 62 U/l (normal range <20 U/l), respectively. A fine-needle aspiration biopsy on a pulmonary lesion revealed a poorly differentiated neuroendocrine carcinoma, negative for PSA and thyroid transcription factor-1 and CgA positive.

The patient was then treated with eight cycles of carboplatin (area under the curve 6) obtaining a partial response of lung lesions (70% decrease on average size) lasting 10 months. When the treatment was stopped, the computerized tomography scan documented the persistence of a partial response. Serum PSA was 5.65 ng/ml and plasma CgA 15.4 U/l. The patient eventually died 18 months from carboplatin treatment start.

Neuroendocrine differentiation in prostate cancer is predictive of poor prognosis [3]. It is notoriously stimulated by ADT as observed both in tumor xenograft [4] and in humans by evaluating prospectively circulating levels of CgA [5]. Our case report indicates that ADT-induced neuroendocrine differentiation could lead to poorly differentiated neuroendocrine carcinoma and in that case, a platinum containing regimen could be potentially more efficacious than docetaxel. It would be interesting to know how many patients in the Loriot et al. series, who responded to cisplatin and etoposide, had poorly differentiated neuroendocrine cancer, unfortunately a tumor biopsy before entering the trial was not carried out.

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