

LONG-TERM RESPONSE TO COMBINATION THERAPY WITH ESTRAMUSTINE AND SOMATOSTATIN ANALOGUE IN A PATIENT WITH ANDROGEN ABLATION-REFRACTORY PROSTATE CANCER

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ABSTRACT

We report on a patient with androgen ablation-refractory prostate adenocarcinoma who had an objective response for longer than 24 months using a combination of estramustine and lanreotide. At baseline from our combination therapy, his prostate-specific antigen level was 21.30 ng/mL and serum chromogranin A level was 816 ng/mL. The patient discontinued complete androgen deprivation therapy and underwent combination therapy with oral estramustine 420 mg/day plus lanreotide acetate 73.9 mg intramuscularly every 4 weeks. After 33 months of follow-up, the patient was alive without clinical disease progression, and his prostate-specific antigen and chromogranin A level was 0.10 and 12 ng/mL, respectively. *UROLOGY* **64**: 1231.e1–1231.e3, 2004. © 2004 Elsevier Inc.

In a previous study,¹ we showed that combination therapy using ethinylestradiol and the somatostatin analogue, lanreotide, offered objective and symptomatic responses in patients with androgen ablation-refractory prostate cancer. We report on a patient who showed a modification in the expression of skeletal metastases, a longer than 24-month objective response, and prostate-specific antigen (PSA) normalization (less than 4 ng/mL) using a combination of estramustine and lanreotide.

CASE REPORT

In April 2000, a 71-year-old man was diagnosed at prostate biopsy with prostate adenocarcinoma with Gleason score 7 (4 + 3). His serum PSA level was 131 ng/mL. A bone scan showed several areas with diffuse skeletal metastases. In April 2000, the patient underwent complete androgen deprivation (CAD) therapy using leuprolin acetate 11.25 mg every 12 weeks plus bica-

lutamide 50 mg daily. In the first period, the patient experienced a clinical response to CAD, demonstrated by a PSA reduction of more than 50% (PSA nadir 0.39 ng/mL). The clinical response to CAD lasted for 11 months. In March 2001, clinical progression during CAD was evidenced by a PSA increase of greater than 50% from the nadir (PSA 14.30 ng/mL). The patient was withdrawn from CAD for 2 months without a clinical response. A new bone scan (Fig. 1) revealed no modification in the skeletal metastases. At progression, his performance status (Eastern Cooperative Oncology Group) score was 3 and his bone pain and analgesic requirement score was 3. In May 2001, the patient discontinued CAD and underwent combination therapy with oral estramustine 420 mg/daily plus lanreotide acetate 73.9 mg intramuscularly every 4 weeks. At baseline from our combination therapy, his PSA level was 21.30 ng/mL and his serum chromogranin A (CgA) level was 816 ng/mL (normal less than 90 ng/mL). After 2 months of follow-up (July 2001), the response to therapy was demonstrated by a PSA normalization (2.64 ng/mL) and CgA decline to less than 50% of the baseline level (CgA 365 ng/mL). In October 2001, a new bone scan revealed a reduction in the intensity of radionuclide uptake at the

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FIGURE 1. Radionuclide bone scan with technetium-99m at progression from CAD. Areas of abnormal uptake of radioactive marker detected in sacral segment of spinal cord, iliac crest bilaterally (more evident in right crest), proximal segment of right femur, and distal left tibial segment.

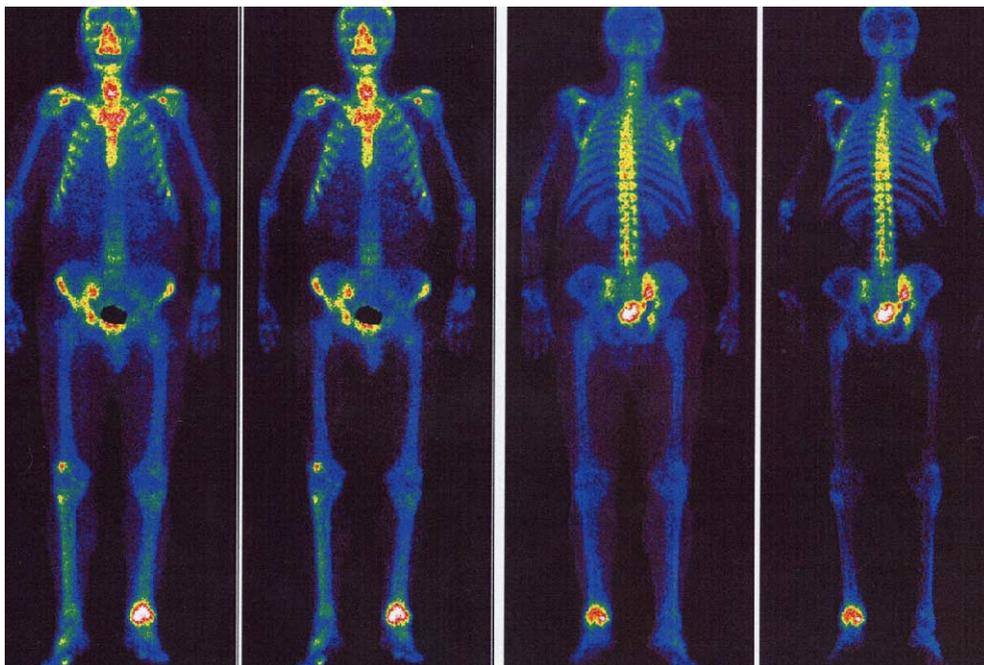


FIGURE 2. Bone scan at response to combination therapy with estramustine plus lanreotide acetate. Reduction in intensity of radionuclide uptake evident, particularly in right iliac crest and sacral segment of spinal cord.

metastatic level (Fig. 2) and a PSA level of 0.06 ng/mL. The clinical response was accompanied by a concomitant reduction in the Eastern Cooperative Oncology Group score (score 1) and bone pain score (score 0). The clinical and symptomatic response remained stable and the CgA levels continued to decrease. After 34 months of follow-up, the patient was still alive without dis-

ease progression. In February 2004, his PSA and CgA level was 0.10 and 12 ng/mL, respectively. His Eastern Cooperative Oncology Group and bone pain score continued to be 1 and 0, respectively (Fig. 3). In March 2004, a new bone scan revealed an additional reduction in the intensity of radionuclide uptake at the metastatic level. No serious side effects from the therapy and no

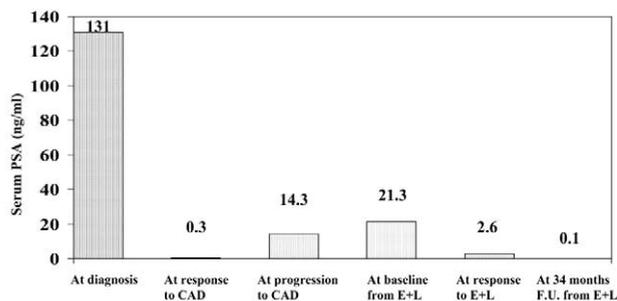


FIGURE 3. Serum PSA levels at different intervals during therapy. E+L = estramustine + lanreotide therapy; F.U. = follow-up.

statistically significant modifications in the laboratory tests were described.

COMMENT

The progression to androgen ablation-refractory (Stage D3) prostate cancer corresponds to cancer cell escape from androgen withdrawal-induced apoptosis. The rationale for our combination therapy in androgen ablation-refractory prostate cancer is to inhibit the protective antiapoptotic effect of the neuroendocrine system on prostate adenocarcinoma cells (somatostatin analogue), to use a new mechanism to induce castration (estramustine), and to add a direct cytotoxic effect on prostate cells (estramustine).¹⁻⁴ The significant reduction in cir-

culating CgA and the negative SRS documented during our therapy suggests that a reduction in neuroendocrine activity on prostate cancer cells is a mechanism accounting for the encouraging and long-term clinical responses observed. In contrast to our previous experience,¹ in this case, we used estramustine and not ethinylestradiol. For the first time, during our therapy, we demonstrated in a patient with Stage D3 prostate cancer a reduction in radionuclide uptake at metastatic sites, accompanied by PSA normalization and progression-free survival for longer than 24 months (34 months). A larger clinical analysis is needed to confirm whether the use of estramustine in our combination therapy is able to improve further the response obtained in patients with limited treatment options and disease refractory to conventional hormonal therapy strategies.

REFERENCES

1. Di Silverio F, and Sciarra A: Combination therapy of ethinylestradiol and somatostatin analogue reintroduces objective clinical responses and decreases chromogranin A in patients with androgen ablation refractory prostate cancer. *J Urol* 170: 1812-1816, 2003.
2. Ernst DS: The role of chemotherapy in advanced prostate cancer. *Can J Urol* 9(suppl 1): 21-25, 2002.
3. Giulligan T, and Kantoff PW: Chemotherapy for prostate cancer. *Urology* 60(3 suppl 1): 94-100, 2002.
4. Sciarra A, Mariotti G, Gentile V, *et al*: Neuroendocrine differentiation in human prostate tissue: is it detectable and treatable? *BJU Int* 91: 438-445, 2003.