

**Reply by Authors.** We thank the correspondents for their interest in our publication, and for further emphasizing the importance of bone health in patients with prostate cancer. Notably, the authors provide evidence that fracture risk in these patients is multifactorial and not solely due to androgen deprivation therapy. Indeed, low bone density is frequently found in patients with prostate cancer before initiation of androgen deprivation therapy. We detected baseline osteopenia or osteoporosis in approximately two thirds of patients entering the United States 2005 study, a population that had received a median of only 3 months of androgen deprivation therapy.<sup>1</sup> While this finding is likely at least partially age related, it also raises the possibility of other contributing genetic or environmental risk factors.

To investigate further, we performed multivariate analyses to evaluate the impact of various lifestyle factors on baseline bone mineral density of the subjects enrolled in the United States 2005 study.<sup>1</sup> We found associations between baseline bone mineral density and body mass index, calcium/vitamin D supplement use and alcohol intake. Thus, while androgen deprivation therapy is clearly a risk factor for accelerated bone loss in our patients with prostate cancer, it is evident that other factors have a role in fracture risk. Further investigation is warranted to understand better the complexities of bone density loss in this disease.

1. Ryan CW, Huo D, Stallings JW, Davis RL, Beer TM and McWhorter LT: Early association between duration of androgen deprivation, life-style factors and bone mineral density in patients with prostate cancer: an analysis during the first 12 months of therapy. *J Urol*, suppl., **173**: 222, abstract 821.

## Re: Clinical and Immunological Characteristics of Patients With Serologic Progression of Prostate Cancer Achieving Long-Term Disease Control With Granulocyte-Macrophage Colony-Stimulating Factor

**B. I. Rini, L. Fong, V. Weinberg, B. Kavanaugh and E. J. Small**

*J Urol* 2006; **175**: 2087–2091.

**To the Editor.** June 2006 saw the publication of the encouraging results of this trial performed at the University of California, in which the potential of granulocyte-macrophage colony-stimulating factor (GM-CSF) as an antitumor agent was tested in patients with prostate cancer. The administration of this agent led to a notable reduction in prostate specific antigen (PSA) and to positive change in terms of PSA duplication time. The authors suggest these results might be due to tumor cells in patients with prostate cancer providing a source of antigen by dendritic cells with subsequent cross-priming of T cells to stimulate a relevant immune response. However, a number of studies have recently suggested that these results could be due more to an innate response involving the action of neutrophils. This possibility deserves consideration, given a recently suggested model of tumor growth dynamics in which neutrophils have a key role in the initial restraint of tumor growth.<sup>1,2</sup>

This phenomenon has been demonstrated experimentally in mice.<sup>3</sup> In addition, when treated with granulocyte colony-stimulating factor to obtain this effect a patient with hepatocarcinoma experienced complete remission.<sup>4</sup> The same phenomenon has also been shown in a strain of mice capable of only an innate immune response (in which the lymphocytes have no role).<sup>5</sup> Also, in a placebo controlled clinical trial in which granulocyte colony-stimulating factor (without macrophage) was administered after surgery and subsequent radiotherapy 5-year survival was greater (84%, compared to 46% in those who received placebo).<sup>6</sup> These results indicate the potential of this agent in preventing relapses. Finally, in a phase II trial the combination of GM-CSF and thalidomide was reported to have antitumor activity in patients with androgen independent prostate cancer.<sup>7</sup> All of these findings indicate this alternative explanation for the action of GM-CSF observed in the University of California study. Urologists should perhaps bear in mind this alternative explanation when interpreting the results of similar studies.

Respectfully,  
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2. Bru A, Albertos S, Subiza JL, Lopez Garcia-Asenjo JA and Bru I: The universal dynamics of tumor growth. *Biophys J* 2003; **85**: 2948.
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4. Bru A, Albertos S, Garcia-Hoz F and Bru I: Regulation of neutrophilia by granulocyte colony-stimulating factor: a new cancer therapy that reversed a case of terminal hepatocellular carcinoma. *J Clin Res* 2006; **8**: 9.
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6. Su YB, Vickers AJ, Zelefsky MJ, Kraus DH, Shaha AR, Shah JP et al: Double-blind, placebo-controlled, randomized trial of granulocyte colony stimulating factor during postoperative radiotherapy for squamous head and neck cancer. *Cancer J* 2006; **12**: 182.
7. Dreicer R, Klein EA, Elson P, Peereboom D, Byzova T and Plow EF: Phase II trial of GM-CSF + thalidomide in patients with androgen-independent metastatic prostate cancer. *Urol Oncol* 2005; **23**: 82.

**Reply by Authors.** We thank Brú for his interest in our recent study regarding the potential role of GM-CSF in the treatment of prostate cancer. Several reports by different groups have documented the clinical and PSA modulating activity of this agent in various prostate cancer disease states.<sup>1–3</sup> However, lacking in all these reports is insight regarding the precise mechanism(s) of antitumor effect and information about the cellular components of any immune response generated. We are unaware of any data regarding granulocyte colony-stimulating factor (without macrophage) in prostate cancer that would implicate granulocytes in the antitumor immune response in this disease. A preliminary report of GM-CSF and thalidomide as neoadjuvant therapy demonstrated posttreatment prostatectomy specimens with

significantly increased T cell and activated dendritic cell infiltration in prostate tumor tissue compared to pretreatment biopsies, implicating these cells in any subsequent PSA modulating effect.<sup>4</sup> Additional tissue based studies of GM-CSF based approaches are required for insight into the mechanism of clinical effect, relevant cellular components and specific antigen targets. We agree that alternative mechanistic explanations must be considered.

1. Rini BI, Weinberg V, Bok R and Small EJ: Prostate-specific antigen kinetics as a measure of the biologic effect of granulocyte-macrophage colony-stimulating factor in patients with serologic progression of prostate cancer. *J Clin Oncol* 2003; **21**: 99.
2. Small EJ, Reese DM, Um B, Whisenant S, Dixon SC and Figg WD: Therapy of advanced prostate cancer with granulocyte macrophage colony-stimulating factor. *Clin Cancer Res* 1999; **5**: 1738.
3. Dreicer R, See WA and Klein EA: Phase II trial of GM-CSF in advanced prostate cancer. *Invest New Drugs* 2001; **19**: 261.
4. Garcia JA, Magi-Galluzzi C, Rothaermel J, Elson P, Zhou M, Klein E et al: Neoadjuvant GM-CSF and thalidomide in men with high-risk prostate carcinoma undergoing radical prostatectomy. *J Clin Oncol*, suppl., 2006; **24**: 4564.

## Re: Safety and Efficacy of Hyperbaric Oxygen Therapy for the Treatment of Interstitial Cystitis: A Randomized, Sham Controlled, Double-Blind Trial

A. van Ophoven, G. Rossbach, F. Pajonk and L. Hertle

*J Urol* 2006; **176**: 1442–1446.

**To the Editor.** We were interested to read the study by van Ophoven et al. However, we are concerned that the article contains some important statistical errors.

The authors describe using chi-square statistics to compare the proportion of responders between groups, with “ $p < 0.05$  considered significant at 80% power.” We do not understand this statement when the authors report that no power calculation was performed.

The authors also report a statistically significant improvement in the primary outcome measure (global response assessment) for the experimental group compared to controls, with a stated  $p$  value of less than 0.05. We repeated the analysis as described in the text using Fisher’s exact test. We used a response rate of 3 of 14 experimental patients, compared to 0 responders in the control group of 7 patients. By our calculation there was no statistically significant difference ( $p = 0.52$ , 2-sided by summation).

In our efforts to account for the discrepancy in these 2 estimates we repeated the analysis including all responders (slightly improved, moderately improved and markedly improved). From the figures presented 9 of 14 patients responded in the hyperbaric oxygen therapy group vs 0 of 7 in the control group. With these figures Fisher’s exact test produces a statistically significant result ( $p = 0.007$ , 2-sided by summation).

We subsequently approached the authors and learned that the journal referees requested a more strict definition of response (moderately and markedly improved only), as described in the published text. We further understand that the

referees asked for inclusion of dropouts (intention to treat). The authors made these changes but failed to update their statistical reporting. We fully agree with the suggestions of the referees but it is unfortunate that an erroneous estimation of statistical significance was published in the final article. Despite this discrepancy, we agree with the conclusion that hyperbaric oxygen therapy may be effective in a subset of patients with interstitial cystitis. The authors have demonstrated statistically significant improvement in pain but not in global response assessment.

Respectfully,

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**Reply by Authors.** We would like to thank Hopson et al for their attentive reading and careful analysis of our study, which revealed a statistical shortcoming. As discussed in the article, the major limitations in analyzing and interpreting our data are the small patient number resulting from the low prevalence of interstitial cystitis (IC) and the complexity and time load of the hyperbaric oxygen (HBO) intervention. For these reasons, and as a result of being a pilot study, we explained that an initial sample size calculation was not performed. The appropriate patient number was determined as much by the feasibility of testing a complex and time-consuming treatment as by statistical considerations. The protocol sample size was judged to provide some feasible indication of whether HBO has any effect on IC symptoms. Under these biomathematical circumstances chi-square statistical analysis is not a valid test for comparison of the proportion of responders, and Fisher’s exact test was applied. We missed giving this information and mistakenly reported an 80% power threshold. The erratum that accompanies our reply will establish coherence.

Regarding the statistical significance of response to treatment, we provided an incorrect number, as pinpointed by Hopson et al. The study protocol characterized patients with symptom improvement of all intensities (slight, moderate and marked) as responders, ie 8 of 12 treated vs 0 of 7 sham patients, following a per protocol analysis ( $p = 0.0128$ , 2-tailed Fisher’s exact test). However, the reviewers asked for intent to treat analysis and requested a stricter definition of responders (moderately and markedly improved). Applying intent to treat instead of per protocol analysis, the latest evaluable post-baseline observation was analyzed for the 2 dropouts, ie 9 of 14 treated vs 0 of 7 sham patients ( $p = 0.0071$ , 2-tailed Fisher’s exact test). Ignoring this last observation carried forward approach, ie 8 of 14 treated vs 0 of 7 sham patients, the results would still have been statistically significant ( $p = 0.0179$ , 2-tailed Fisher’s exact test). However, the statistical significance following the stricter definition of responders and resulting in the reported 3 of 14 treated vs 0 of 7 sham patients ( $p = 0.5211$ , 2-tailed Fisher’s exact test) was not updated, and the aforementioned significances were misapplied and misreported. The erratum that accompanies our reply to the editor will establish coherence regarding this aspect as well.

Finally, we fully agree with the authors that HBO consistently shows efficacy in daily work. We are happy to be able to offer HBO to our patients with IC as an innovative and noninvasive therapeutic approach that does not cause structural damage to the bladder.