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Letters to the Editor

Pituitary Gland Metastases

To the Editor:

The article by Sioutos et al (1) provides important information on the symptoms caused by pituitary gland metastases. I draw your attention to an old publication describing another interesting effect of pituitary gland metastases.

In a Dutch journal in 1965 (2) I described three patients with breast carcinoma who manifested diabetes insipidus during the course of their disseminated breast cancer and showed after the onset of the diabetes insipidus a striking improvement in disability from the metastases. These improvements could not be attributed to medical treatment. All three patients were in the terminal stages of metastatic carcinoma (skin metastases, regional metastases, pleuritis carcinomatosa, and bone metastases). The patients were 43, 53, and 55 years of age. In the youngest patient, the course before spontaneous remission was so rapidly progressive that hormonal therapy was not attempted. The 53-year-old patient had had a remission of 6 months on ovariectomy and prednisone therapy; and the 55-year-old patient had had a brief remission after androgen treatment. The disease again became progressive in these two patients before the appearance of signs of diabetes insipidus. None of the patients had been treated with cytotoxic drugs. Spontaneous improvement in the symptoms, recalcification of osteolytic foci, regression of cutaneous and lymph node metastases, and disappearance of the carcinoma pleuritis began shortly after the onset of the diabetes insipidus. In two cases, the rate of tumor growth was thought to be rapid, and spontaneous remission was of relatively short duration (6 months). In contrast, remission in the oldest patient lasted for 2 years. In all three cases, there was an associated diabetes insipidus that responded favorably to Piton sniff. In one patient, the diabetes insipidus slowly disappeared. In two patients, radiologic examination showed distinct destruction of the sella turcica area. Various functional tests confirmed hypofunction of the pituitary. In one patient autopsy was performed, which showed that the pituitary had a normal aspect but was invaded entirely by tumor tissue.

This peculiar phenomenon of "therapeutic" impact of the pituitary gland metastases in hormone-dependent tumors was not mentioned in the otherwise important article of Sioutos et al.

J. A. van Dongen
The Netherlands Cancer Institute
Amsterdam, The Netherlands

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Multi-institutional Melanoma Vaccine Trial

To the Editor:

In the article by Wallack et al. (1), the authors conclude that subset analysis of a randomized phase III vaccine trial "shows encouraging survival benefits in certain subsets of patients and an increasing trend in overall survival." The authors go on to state in their discussion that "the subset of patients with clinical stage I, pathologic stage II disease had a definite survival advantage on VMO when compared with V" and that "male patients who are <57 years of age and who have one to five positive nodes had improved survival on VMO." They state uncategorically that "even though these results are not statistically significant, they are both interesting and compelling."

This characterization of the results of these subset analyses is simply unfounded. These results are most definitely not compelling, as the conclusions made in this article are not justified by the data presented. The authors have violated fundamental principles governing the analysis of treatment effects in subgroups of patients in randomized clinical trials. These principles have been enumerated by Yusuf et al. (2). The most fundamental flaw is the use of data-derived subgroups, which were not incorporated into the design of the trial. The selection of males <57 years of age with one to five positive nodes has no biologic, clinical, or scientific rationale whatsoever. It was evidently chosen only because it gave the lowest possible p value the authors could find. Even with this unjustified subgroup analysis, the result did not achieve statistical significance. From a statistical standpoint, none of the appropriate statistical comparisons for this type of trial (such as global tests for interactions among pre-defined subsets) are presented, nor is there any indication of whether or not p values were adjusted for the multiple comparisons that must have been performed before the subgroup of males <57 years of age with one to five positive nodes was finally discovered to be nearly but not quite significant.

It is possible that active, specific immunotherapy will one day be shown to have a beneficial role in the treatment of patients with resected malignant melanoma. That

day will only come when properly conducted randomized trials show an overall improvement in disease-free survival and survival that is statistically significant. This trial did not do so.

Vernon K. Sondak, MD
Associate Professor of Surgery
University of Michigan Medical Center
Ann Arbor, Michigan

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Authors' Reply

To the Editor:

We thank Dr. Sondak for his review of our article.

This study was the first ever randomized prospective double blind Melanoma Vaccinia Oncolysate (VMO) Vaccine trial that was both FDA and NCI approved and funded. Bias was eliminated by making the placebo (vaccinia vaccine virus) resemble the VMO so that neither the patient nor the doctor knew which treatment was being given. Furthermore, the vaccine distribution center and the trial biostatistical center were located at an institution far removed from the principal investigator's institution to further eliminate investigator bias. We believed the trial was well organized and designed and we hope that it will serve others as a strong model for organizing and performing future cancer vaccine trials. Thus, even though the results of the first interim analysis were not statistically significant in showing either an improvement in disease-free interval or survival, we did believe that by performing a retrospective analysis of the data, we could find some interesting hypothesis in the subsets that we could use as a base for designing future melanoma vaccine trials. We certainly stated this rationale very clearly in the articles that we have written on this trial, and we never claimed statistical significance. As a result of this decision, subsets of all male patients >57 years old with one to five positive nodes, and subsets of patients who had clinical Stage I and pathological Stage II disease were identified as showing a higher survival rate with VMO than with V. The survival curve of these subsets exhibited a trend in survival in favor of the VMO therapy which perhaps could be important for future vaccine trial designs and could demonstrate that perhaps melanoma vaccines could act differently on patients at the same stage, depending upon age and sex. Moreover, we do recognize that the multiple testing issues and the p values for these subset analyses have little value, as the trial was not designed prospectively with enough patients to test vaccine efficacy in these subsets. However, again, we do state that the reason for doing this analysis is to perhaps alert future investigators that they may want to design randomized prospective melanoma trials with more subsets. Furthermore, [in an article published in the Journal of the American College of Surgeons, September 19, 1995, Vol. 181, 193–201] Barth et al. (1) clearly review the various characteristics of approximately 1,521 stage IV melanoma patients in their data base and show that when one begins to consider prognostic factors in melanoma, it may be important to consider age and sex as well as tumor location and depth of invasion. Although it seems that depth of invasion and the number of positive nodes may be the most important factors for AJCC stage III disease, we thought that it was fascinating that in our trial there were trends that showed the importance of sex, age, and clinical and pathologic stage.

Lastly, it is important to note that our trial was severely limited by regulatory conditions placed on it by the FDA. As is well known, this randomized, prospective trial in which a new adjuvant therapy was tested in a surgical adjuvant study in a human tumor model that had no other adjuvant therapy at the time of trial development should have been designed with a no-treatment arm. However, the FDA refused to allow us to have a no-treatment arm in this AJCC Stage III melanoma randomized trial. As a result, we were forced to use one of the components of the vaccine, vaccinia virus, as the placebo. Interestingly, this arm in and of itself may have had some activity, and as a result, we cannot really compare our results currently with those of other trials that used a no-treatment arm.

Therefore, there is work yet to be done. Although it took 20 years to complete this trial for the first generation VMO, we do plan to design another trial with a second generation vaccine. Moreover, we do hope to benefit from what we learned in our first trial, and we can only benefit from these data if, and only if, the work continues to be reviewed and published in appropriate journals.

Marc K. Wallack, MD
Professor and Chairman
Department of Surgery

Muthukumaran Sivanandham, PhD
Director
Surgical Research Laboratory
Saint Vincents Hospital
and Medical Center
New York, New York

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