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The Provenge® decision

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On 9 May 2007 the FDA decided not to approve the prostate cancer vaccine Provenge® (Dendreon Corporation, Seattle, WA), despite the recommendation to approve it by its own advisory committee. This decision was taken because the two small studies presented to the advisory committee, one of which has been published, failed to meet their primary end points (Small EJ *et al*. [2006] *J Clin Oncol* 24: 3089–3094). The company that produces Provenge® also tacitly admitted the lack of evidence of efficacy by initiating a larger study, which is near completion, to test survival as the primary end point. The FDA wisely chose to wait until these data are available before approval.

The real question is not why the FDA failed to approve the vaccine, but rather why they agreed to review the data in the first place. The furor surrounding the FDA decision perhaps informs us. Winston Churchill was fond of saying that wherever there is free speech, there is also a lot of foolish speech, and this was certainly the case before and after the FDA decision. During the review process, patient advocacy groups cheered and applauded people who made positive statements about the vaccine and expressed their displeasure at less than positive statements, as if it were a football match. This was patient advocacy at its worst. A member of the FDA advisory committee made a statement indicating that even though the primary end points were not met, the vaccine should be approved because it was breaking new ground. An article was published the next day in the *Wall Street Journal* by the Chief Executive Officer of Pharmacyclics. His article was more a diatribe against the FDA for its failure to approve his company's own relatively nontoxic drug, than a logical critique of the FDA decision.

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It is easy to understand how patients and their advocates can be seduced by the age old lure of a harmless drug stimulating the immune system. Purveyors of unproven remedies have preyed on this feeling for years. Even clinical investigators have succumbed to it. The use of BCG in the 1970s to stimulate the immune system of patients with cancer set the field of immunotherapy back a decade.

I am normally very much in favor of patients having access to drugs that show promise, but are not yet approved by the FDA. So, what is the harm here of approving a fairly nontoxic vaccine like Provenge®? The harm is twofold. First, the promise of Provenge® does not derive from positive data in the two studies presented. It derives from the attractive concept of having a vaccine that will stimulate the patient's immune system. That is a dangerous precedent. There are actually other drugs in the pipeline that show more promise, at the moment, than Provenge®, in patients with advanced prostate cancer. The second difficulty derives from the fact that the FDA has unfortunately assumed the role of the oncologist of last resort (DeVita VT [2005] *Nat Clin Pract Oncol* 2: 423). In approving Provenge® it would establish a new standard of care and force all other new therapies into head-to-head trials for their approval. This situation would slow, not accelerate the development of new drugs.

Those of us who want the FDA to recognize that cancer is different from the common cold and hypertension, and that cancer drugs, and access to them, should be judged by a different set of standards to those used for other drugs, need to be very careful. If we cheer and support the approval of drugs or biologics at a point when there is no substantial evidence of efficacy we will not be taken seriously when it really counts.