Re: Interdisciplinary Critique of Sipuleucel-T as Immunotherapy in Castration-Resistant Prostate Cancer

A recent article by Huber et al. (1) published in the Journal discussed a number of study design issues regarding the pivotal phase III trial of sipuleucel-T published in the New England Journal of Medicine (2) in 2010. Although the commentary by Huber et al. raises several controversial topics, the authors raise a concern about the characteristics of T cells responding to transient lymphopenia via homeostatic proliferation (HP), stating as follows: “Homeostatic proliferation and migration of peripheral T-cells might maintain the absolute numbers in the circulation, but the resultant population would differ from the unperturbed population in important functional ways” (1). However, this statement is misleading because a large body of published data suggests that T cells responding to HP are in fact more functional than their nonproliferating counterparts, and they acquire an effector phenotype during the process (3–6). A particularly relevant study in an animal model of melanoma showed that homeostatic proliferation alone can be sufficient to mediate an antitumor immune response (4). More recent work shows that even deeply tolerized CD8+ T cells can be functionally restored by HP (7). Studies are not limited to animal models; an important component of an evolving T-cell transfer immunotherapy regimen developed by Dudley et al. (8) includes lymphodepletion of the host, such that infused cells respond by proliferating and acquiring effector function. This regimen, although still experimental, is one of the most effective published in the melanoma field. In summary, the homeostatic proliferation that likely occurs in response to transient lymphopenia experienced by sipuleucel-T patients during leukopheresis would be expected to drive, rather than to impede, a potential antitumor immune response.

CHARLES G. DRAKE

References

Notes
C. G. Drake has served as paid consultant for Dendreon, Inc, the manufacturers of sipuleucel-T. He has also consulted (reimbursed) for Bristol Myers Squibb (BMS) and Amplimmune, Inc, and has licensed patents to BMS and Amplimmune, Inc.

Affiliation of the author: Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD.

Correspondence to: Charles G. Drake, MD, PhD, Department of Oncology, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans St, CRB I #410, Baltimore, MD 21231 (e-mail: cdrake@jhmi.edu).

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Response
We appreciate the opportunity to respond to Dr Drake’s correspondence. Our commentary highlighted several clinically significant interactions between age and survival in the sipuleucel-T trials that conflict with expectations. These data, which came from a subset analysis that was prespecified for the IMPACT trial, had not previously been published (1). Since publication, defenders of sipuleucel-T have provided no explanations for these unprecedented and counterintuitive results. We maintain our belief that potential harm caused to older patients by the differential depletion of mononuclear cells from the trial groups could account for the unexpected age data, the lack of a measurable response to sipuleucel-T, and the overall survival results.

We had proposed that after a patient’s circulating lymphocytes recover from depletion, “the resultant population would differ from the unperturbed population in important functional ways.” Drake impugns our statement as “misleading,” but six studies cited in his correspondence support it. He cites five animal studies focusing exclusively on CD8+ T cells, which do not consider age, whereas we cited evidence showing age-related impairments of eight other aspects of adaptive immunity. Active lymphocyte depletion might exacerbate any or all of these impairments, several of which have been observed in human studies of leukopheresis (Table 1) (2–6). These impairments might have particularly harmful consequences in elderly patients with metastatic cancer.

Drake also cites a melanoma study in which patients were immunodepleted before the infusion of lymphocyte cultures reactive to their tumors. We find this study of little relevance for three main reasons. First, in contrast to prostate cancer, metastatic melanoma is highly immunogenic, so the concept of augmenting the T-cell response to “nonself” melanoma antigens has a sound immunological basis. However, T cells with high affinity for “self” antigens are deleted in the thymus prior to maturation (7). Overexpression of the gene for prostatic acid phosphatase in the thymus ensures that T cells with high affinity for the prostatic acid phosphatase protein do not emerge. Thus, we find the proposed mechanism for sipuleucel-T improbable because the crucial interaction...