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

Huber et al. made three observations related to the phase III IMPACT trial leading them to suggest that the observed difference in overall survival (OS) could have been attributed to age-dependent immunodepletion resulting from leukapheresis of the control arm patients (1). Evidence from the sipuleucel-T trials and the literature refute this alternative explanation.

Observation 1: Two Unexpected Interactions Between Patient Age and Survival

Studies have shown age to be prognostic in castration-resistant prostate cancer (2,3). Most studies investigating prognostic factors in castration-resistant prostate cancer have focused on chemotherapy-treated patients in whom other prognostic factors might be expected to outweigh age. The sipuleucel-T studies exclusively enrolled patients with asymptomatic or minimally symptomatic disease, 85% of whom were chemotherapy naïve (4,5). In a pooled analysis of these studies, age (in 10-year increments) was a statistically significant predictor of OS in both sipuleucel-T (hazard ratio [HR] of death = 1.28, 95% confidence interval [CI] = 1.12 to 1.47) and control (HR of death = 1.31, 95% CI = 1.10 to 1.56) arms (Dendreon data on file), which would not be anticipated if the control group had experienced relative immunodepletion.

Among 63 subgroups assessed for the IMPACT study report, OS favored sipuleucel-T (ie, a HR of death < 1.0) in all subgroups including above and below the median age of 71 (4); only the subgroup of patients aged less than 65 years did not favor sipuleucel-T. Given the high probability of a false-positive result with this number of subgroup analyses, it is important to seek additional data for consistency. In an analysis of the first two phase III sipuleucel-T trials, positive treatment effects were observed in patients less than 65 years of age (HR of death = 0.57, 95% CI = 0.27 to 1.21) and 65 years or older (HR of death = 0.69, 95% CI = 0.49 to 0.98), with the trend actually favoring a greater treatment effect in the younger subgroup (Dendreon data on file). Furthermore, when both IMPACT and the earlier phase III studies are dichotomized at the median age of 71, the treatment effect of sipuleucel-T is consistent in both the younger and older patients (4,5).

The US Food and Drug Administration (FDA) performed an analysis of pooled data across the three phase III sipuleucel-T trials and obtained a favorable estimate for the treatment effect in patients younger than 65 years (HR of death = 0.92, 95% CI = 0.62 to 1.37). The FDA reviewers’ conclusion was that the “… analyses of the data from all three studies … support the hypothesis that the subgroup of patients who were less than 65 years of age also benefit from treatment with sipuleucel-T. The hazard ratio in the subgroup of Study D9902B [IMPACT] patients who were less than 65 years of age most likely resulted from chance, related to the multiplicity of comparisons…” (6).

Observation 2: Older Patients in the Placebo Group Appear to Have Shorter OS Than Might Be Expected From Other Studies

A review of recent trials with patient populations comparable to that in IMPACT demonstrates consistency of the median survival of the control arms, ranging from 16.6 to 21.5 months (Table 1) (4,7). Huber et al. (1) cited the 27.1-month median OS of IMPACT control patients with a more than 18-month Halabi-predicted survival (n = 114); at 26.7 months, it compares favorably to the median OS of control patients from the GVAX subset analysis, particularly given that the GVAX control arm involved active treatment with docetaxel. Furthermore, the definition of “minimally symptomatic” used for the subgroup of patients from TAX327 who had a 25.6-month median OS (n = 110) included a minimal score on a quality-of-life questionnaire (8), which was not included in the IMPACT definition. A larger TAX327 minimally symptomatic subgroup (n = 550) that did not include the quality-of-life criterion for defining symptomatology revealed a median survival of 21.3 months for all three treatment arms combined (Table 1) and 19.8 months specifically in the control arm (9).

Observation 3: Potential Harm From the IMPACT Study Interventions

Huber et al. (1) failed to account for the fact that the intravascular pool of mononuclear cells represents a small fraction of the total body pool and that these populations rapidly reequilibrate (10). The 1.5–2.0 volume leukapheresis procedure in IMPACT removed approximately $7 \times 10^9$ lymphocytes. Given that the total body pool of lymphocytes is estimated between $5 \times 10^{11}$ and $6 \times 10^{12}$ cells (11-13), leukapheresis removed only 0.1%–1.4% of the total number of lymphocytes. This small percentage would not be expected to have any substantive effect on the lymphocyte repertoire.

An extensive body of literature has shown no detrimental effects of repeated apheresis procedures on healthy donors (14), and the median white blood cell, neutrophil, lymphocyte, and monocyte counts in the sipuleucel-T studies were within normal ranges at 2, 10, and 22 weeks following the third leukapheresis procedure in both the sipuleucel-T and the control groups (15). Furthermore, cells undergoing
homeostatic proliferation actually tend to be more, rather than less, immunoreactive, as evidenced by multiple cancer immuno-therapy protocols that induce lymphopenia before immunization and/or adoptive T-cell transfer to augment immune activation and clinical efficacy.

Finally, infection-related adverse events were not increased among the control arm and were consistent with what would be expected in an elderly population over an extended period of follow-up (15). The storage of the cells from the control group did not lead to infusion of dead cells, because the median viabilities were greater than 95% for both sipuleucel-T and control groups (Dendreon unpublished data on file).

Table 1. Key prognostic factors and outcomes from clinical trials of patient populations comparable to those enrolled in IMPACT (4,7)*

<table>
<thead>
<tr>
<th>Study†</th>
<th>IMPACT</th>
<th>Prostvac minimally symptomatic subgroup</th>
<th>Zibotentan</th>
<th>ASCENT-2</th>
<th>Atrasentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>341</td>
<td>171</td>
<td>82</td>
<td>40</td>
<td>550</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>25.8</td>
<td>21.7</td>
<td>25.1</td>
<td>16.6</td>
<td>21.3</td>
</tr>
<tr>
<td>Prognostic features</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age, y</td>
<td>72</td>
<td>70</td>
<td>71.5</td>
<td>79</td>
<td>NR</td>
</tr>
<tr>
<td>Narcotic free, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Prior chemotherapy, %</td>
<td>19.6</td>
<td>15.2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PSA (ng/mL), median</td>
<td>51.7</td>
<td>472</td>
<td>36</td>
<td>45</td>
<td>NR</td>
</tr>
<tr>
<td>LDH (u/L), median</td>
<td>194</td>
<td>193</td>
<td>194</td>
<td>205</td>
<td>NR</td>
</tr>
<tr>
<td>Alk Phos (u/L), median</td>
<td>99</td>
<td>109</td>
<td>100</td>
<td>115</td>
<td>NR</td>
</tr>
<tr>
<td>Gleason score≤7 , %</td>
<td>75.4</td>
<td>75.4</td>
<td>100</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>ECOG 0–1, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>NR</td>
</tr>
<tr>
<td>Hemoglobin (g/dL), median</td>
<td>12.9</td>
<td>12.7</td>
<td>13.0</td>
<td>12.7</td>
<td>NR</td>
</tr>
<tr>
<td>Visceral disease, %</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td>Study funding</td>
<td>Dendreon</td>
<td>Bavarian Nordic</td>
<td>Sanofi-Aventis</td>
<td>Astra-Zeneca</td>
<td>Novacea</td>
</tr>
</tbody>
</table>

* Alk Phos = alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group performance status scale; LDH = lactate dehydrogenase; NR = not reported; OS = overall survival; PSA = prostatic specific antigen.
† In the IMPACT trial, sipuleucel-T (S) was compared with a control intervention (C). In the prostvac trial, recombinant vaccinia vector-PSA-TRICOM (2 × 10⁶ pfu) followed by recombinant Fowlpox-PSA-TRICOM boost (1 × 10⁹ pfu) + recombinant granulocyte-macrophage colony-stimulating factor adjuvant (PV) was administered to patients and was compared with patients who received the control intervention (C). Patients in the Tax 327 trial were administered 75 mg/m² docetaxel every 3 weeks + 5 mg prednisone twice daily (D3P) and were compared with both patients who received 30 mg/m² docetaxel weekly + 5 mg prednisone twice daily (D1P) and those who received 12 mg/m² mitoxantrone every 3 weeks + 5 mg prednisone twice daily (MP). No previous therapy with chemotoxic agents with the exception of estramustine, which was allowed. The clinical trial of zibotentan compared patients who received 15 mg zibotentan daily (Z15) with those who received 10 mg zibotentan daily (Z10) and those who received an oral placebo daily (P). In the ASCENT-2 trial, the treatment arms were high-dose calcitriol daily + 36 mg/m² docetaxel every 3 weeks + 8 mg oral dexamethasone 12 hours, 3 hours, and 1 hour before docetaxel infusion for 3 of 4 weeks (CD1) vs prednisone twice daily + 75 mg/m² docetaxel every 3 weeks and 8 mg oral dexamethasone 12 hours, 3 hours, and 1 hour before docetaxel infusion (PD3). Prior chemotherapy (only estramustine monotherapy) was allowed. The atrasentan trial compared 10 mg atrasentan daily (A) vs oral placebo daily (P). The median Gleason score in both treatment arms was 7, percentage of patients with Gleason score of 7 or lower was not reported. ECOG was not reported; the value listed for ECOG 0–1 represents the percentage of patients with Karnofsky Performance Status 100–80.

Conclusions
The control arm intervention for the sipuleucel-T trials was chosen after careful consideration and discussion with the FDA. Having patients in the control arm undergo leukapheresis procedures and subsequent infusion of a cellular product that was identical in appearance to sipuleucel-T substantially strengthened the study design and the interpretability of the results.

The sipuleucel-T data have undergone rigorous review, including an FDA advisory committee, FDA review, a Center for Medicare and Medicaid Services national coverage determination, a Technology Assessment, and the peer review of multiple publications. The issues raised by Huber et al. were considered during these reviews and not given credence.

PHILIP W. KANTOFF
CELESTIA S. HIGANO
ERIC J. SMALL
JAMES B. WHITMORE
MARK W. FROHLICH
PAUL F. SCHELLHAMMER
ON BEHALF OF THE IMPACT AUTHORS
References

Funding
No author has received financial support for the submitted work. The IMPACT trial was funded by Dendreon Corp.

Notes
P. W. Kantoff served as a paid consultant for Bellicum, BN-IT, Janssen, Bayer, Sanofi-Aventis, and Dendreon Corp. C. S. Higano has served as a paid consultant for Amgen, Astra Zeneca, Bayer, Bristol-Myers Squibb, Medivation, Millennium, Sanofi-Aventis, Teva, and Dendreon Corp; received research funding from Amgen, Bayer, Cell Genesys, Cougar, Imclone, Medivation, Millennium, Sanofi-Aventis, Teva, and Dendreon Corp; received honoraria from Amgen, Astra Zeneca, Bayer, Bristol-Myers Squibb, Medivation, Millennium, Sanofi-Aventis, Teva, and Dendreon Corp; her spouse is cofounder of Cell Therapeutics, Inc. E. J. Small has received honoraria from Celgene Corp, F Hoffman-La Roche Ltd, J&J Pharma Serv, LLC, Millennium, and Dendreon Corp and has received other remuneration from Dendreon Corp. J. B. Whitmore and M. W. Frohlich are employees of Dendreon Corp. P. F. Schellhammer has received honoraria from Amgen, Astra Zeneca, Bayer, and Dendreon Corp. The authors thank Johnathan C. Maher, PhD, of Dendreon Corp for contributing to the writing and editing of the manuscript, and approved the final version for submission.

Affiliations of authors: Genitourinary Oncology Program, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA (PWW); Seattle Cancer Care Alliance, School of Medicine, University of Washington, Seattle, WA (CSH); Urologic Oncology Program, University of California San Francisco, San Francisco, CA (EJS); Dendreon Corporation, Seattle, WA (MWF); Department of Urology, Eastern Virginia Medical School, Norfolk, VA (FPS).

Correspondence to: Philip W. Kantoff, MD, Dana-Farber Cancer Institute, Harvard Medical School, 450 Brookline Ave, Boston, MA 02215 (e-mail: Philip.Kantoff@dfci.harvard.edu). DOI:10.1093/jnci/djs279 ©The Author 2012. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

Response
We thank both Gulley et al. and Kantoff et al. for their interest in our article and appreciate this opportunity to respond. It is a principle of phase III clinical trials that a new intervention is compared with the best standard of care. The mere possibility that a “placebo” intervention might be harmful should be enough to discredit a trial. The onus, therefore, lies with advocates of sipuleucel-T to prove that the control intervention in the IMPACT trial was harmless.

Age and Survival
Both correspondences protested our use of the subgroup overall survival (OS) data, yet their focus on hazard ratios distracts from our primary concern about the shorter survival of older patients in the sipuleucel-T trials. In all three prognostic models for this population (1), and all large, recent phase III trials with available analyses—including docetaxel, calcitriol, cabazitaxel, abiraterone, and atarantus—age was not prognostic of survival (2–4). This stands in stark contrast with the sipuleucel-T trials, in which the prognostic value of age for survival was clinically and statistically significant. Kantoff et al. also called this a “new finding” in their poster and podium presentations at the 2010 American Society of Clinical Oncology Annual Meeting, which showed an unprecedented 2.6% increase in the hazard of death per year of age (P < .001) (5).

We maintain that harm to older patients from immunodepletion in the trial interventions might explain this aberration. The unpublished data in Kantoff et al.’s correspondence showing age was predictive of survival in both arms supports our contention as both treatment groups sustained substantial lymphodepletion (only a median of 10% and 31% of harvested mononuclear cells were subsequently returned in the placebo and sipuleucel-T infusions, respectively).

Yet Kantoff et al. now write that age is prognostic after all, citing a pain-stratified reanalysis of three CALGB trials conducted in the 1990s that excluded 22% of patients. But when all patients were included, Halabi’s original analysis of these trials found no age effect (1).

“Evaluable Evidence” from Other Studies
To correctly interpret the IMPACT trials, it is critical to determine the safety of lymphocyte depletion. The studies cited in Table 1 (6–11) identified numerous adverse