



Invited Commentary | Oncology

Postmarketing Analysis of Sipuleucel-T—The Importance of Real-World Data

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Sipuleucel-T was the first autologous cellular immunotherapy approved by the US Food and Drug Administration (FDA) in 2010 and is used in the treatment of patients with metastatic castration-resistant prostate cancer.¹ Sipuleucel-T demonstrated a 4-month overall survival benefit for patients with asymptomatic or minimally symptomatic disease in a randomized clinical trial.¹ Dores et al² analyze reports to the FDA's Adverse Event Reporting System to examine adverse events in patients who have received sipuleucel-T as reported by health care professionals, consumers, and manufacturers. This postmarketing analysis identified several adverse events that were more common among patients receiving sipuleucel-T compared with all other patients in the database, confirming important adverse events described in the initial clinical trials and package materials. These include infusion-related reactions, infections, and thromboembolic events. Dores et al² provide additional evidence that sipuleucel-T is generally safe and is not associated with previously unrecognized adverse events.

Understanding the safety profile of sipuleucel-T is critically relevant to the care of patients with metastatic castration-resistant prostate cancer. The potential risks and long-term adverse events associated with sipuleucel-T are not well known, because sipuleucel-T is the first autologous cellular immunotherapy, it was approved less than a decade ago, and only 1 in 10 patients with metastatic castration-resistant prostate cancer receive sipuleucel-T.³ Consequently, few practices will have enough experience to recognize and attribute rare complications to this novel therapy. The FDA's Adverse Event Reporting System serves as an important resource to gather real-world safety experience and outcomes of patients receiving sipuleucel-T.

Although an overall survival benefit was seen in clinical trials,¹ sipuleucel-T treatment is rarely associated with significant changes in prostate-specific antigen levels, in the radiographic assessment of tumor burden, or in progression-free survival.⁴ Without reliable biomarkers or surrogate outcome measures, clinicians rely on patient characteristics to identify appropriate patients. Therefore, understanding patterns of serious adverse events using real-world data will provide additional information to identify patients who are best suited for sipuleucel-T. For example, infections were reported disproportionately in patients receiving sipuleucel-T.² If central venous catheter use can be avoided, perhaps complications such as line infections can also be decreased. In addition, patients at high risk for thromboembolic events or with multiple risk factors for cerebrovascular or myocardial events may not be ideal candidates for sipuleucel-T. Further reports from the Provenge Registry for Observation, Collection, and Evaluation of Experience Data (PROCEED)^{5,6} are also expected to help optimize patient selection.

Postmarketing analysis may also inform sequencing strategies for patients with metastatic castration-resistant prostate cancer. Since 2010, additional agents such as cabazitaxel, abiraterone, enzalutamide, and radium 223 dichloride have been approved by the FDA. Sipuleucel-T was approved on the basis of efficacy data in patients with asymptomatic or minimally symptomatic disease. It is notable that in the FDA's Adverse Event Reporting System, 128 patients died within 30 days of infusion.² In contrast, less than 1% of patients died within 30 days in the preapproval clinical trials.¹ This highlights significant differences in the use of sipuleucel-T outside of clinical trials. For the 35.6% of these deaths in the FDA's Adverse Event Reporting System that were attributed to prostate cancer, patients received the drug too late to derive benefit.² Sipuleucel-T would ideally be

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sequenced before the development of significant symptoms to allow for adequate time for the treatment to work. Similarly, as patients develop symptoms, other treatments should be prioritized.

This study by Dores et al² could change practice in 2 ways. First, these data serve as a call for clinicians to report adverse events to the FDA's Adverse Event Reporting System. Contributing individual patient outcomes data advances the collective understanding of the safety of medications for patients. Second, Dores et al² demonstrate that many patients who received sipuleucel-T differ from those included in clinical trials. This real-world experience can help clinicians decide whether the efficacy seen in clinical trials translates to effective treatments for patients. Taken together, understanding patient outcomes can help optimize patient selection and minimize the toxic effects of treatments for patients with advanced prostate cancer.

ARTICLE INFORMATION

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REFERENCES

1. Kantoff PW, Higano CS, Shore ND, et al; IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med*. 2010;363(5):411-422. doi:10.1056/NEJMoa1001294
2. Dores GM, Bryant-Genevier M, Perez-Vilar S. Adverse events associated with the use of sipuleucel-T reported to the US Food and Drug Administration's Adverse Event Reporting System, 2010-2017. *JAMA Netw Open*. 2019;2(8):e199249. doi:10.1001/jamanetworkopen.2019.9249
3. Caram MEV, Ross R, Lin P, Mukherjee B. Factors associated with use of sipuleucel-T to treat patients with advanced prostate cancer. *JAMA Netw Open*. 2019;2(4):e192589. doi:10.1001/jamanetworkopen.2019.2589
4. Beer TM, Bernstein GT, Corman JM, et al. Randomized trial of autologous cellular immunotherapy with sipuleucel-T in androgen-dependent prostate cancer. *Clin Cancer Res*. 2011;17(13):4558-4567. doi:10.1158/1078-0432.CCR-10-3223
5. Armstrong AJ, Higano CS, Sartor AO, et al. Changing characteristics of patients treated with sipuleucel-T (sip-T) over time: real-world experience from the PROCEED registry. *J Clin Oncol*. 2016;34(2)(suppl):320. doi:10.1200/jco.2016.34.2_suppl.320
6. Sartor AO, Oliver Sartor A, Armstrong AJ, et al. Overall survival (OS) of African-American (AA) and Caucasian (CAU) men who received sipuleucel-T for metastatic castration-resistant prostate cancer (mCRPC): final PROCEED analysis. *J Clin Oncol*. 2019;37(15 suppl):5035. doi:10.1200/jco.2019.37.15_suppl.5035