Methodological Review by Lillian S. Kao, MD, MS, and Robert E. Lasky, PhD

Article Reviewed


Review

On first examination, the IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial by Kantoff et al\textsuperscript{5} addresses the following question: among patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer and an expected survival of at least 6 months, does treatment with sipuleucel-T versus placebo result in increased overall survival? However, patients randomized to the placebo group were allowed to enroll in an open-label salvage protocol after assessment of disease progression and receive APC8015F, which was a product manufactured from cryopreserved cells to the same specifications as sipuleucel-T. Thus, the question addressed should instead be stated as: among patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer and an expected survival of at least 6 months, does treatment with sipuleucel-T versus placebo followed by optional APC8015F result in increased overall survival? The trial reported improved overall survival in the sipuleucel-T group with a 22% relative risk reduction in death and an increase in median survival of 4.1 months, but no difference in time to objective disease progression.

Are the results valid?

Randomization was performed in a 2:1 allocation ratio (of sipuleucel-T to placebo) and stratified for primary Gleason grade (≤3 or ≥4), the number of bone metastases (≤5, 6-10, or >10), and bisphosphonate use (yes or no). The follow-up surveillance protocol for disease progression was similar in both groups. The primary outcome was overall survival, and the secondary outcome was time to objective disease progression on the basis of radiographic studies as determined by a blinded, independent radiology-review committee. The trial enrolled 512 patients and had 331 deaths by the data-cutoff date; the estimated sample size was 500 patients with 304 deaths in order to have 20% power to detect a 31% relative risk reduction in death.

There are three design features to this trial that are worth expanded discussion: (1) the change in primary outcome after the trial began, (2) potential modification of effect by post-study treatments such as docetaxel, and (3) the allowance of patients randomized to placebo to “crossover” or receive APC8015F.

Change in primary outcome

The co-primary endpoints of the trial as originally designed were time to objective disease progression and time to disease-related pain. However, the authors state that “after a review of survival results from two previous phase 3 trials with a similar design and before the unblinding of group assignments in our study, we made overall survival the primary end point; the time to objective disease progression became a secondary endpoint and the time to disease-related pain was eliminated.”\textsuperscript{1}
The two prior trials, D9901 and D9902A, were two identically designed randomized trials evaluating the safety and effectiveness of sipuleucel-T. D9901 enrolled 127 patients from January 2000 to October 2001. Sipuleucel-T was associated with a non-significant increase in time to disease progression as compared to placebo and an increase in overall survival of 25.9 months versus 21.4 months. D9902A enrolled 98 patients from May 2000 to March 2003, at which point enrollment was stopped after obtaining the disease progression results, but not the survival results from D9901. The results from D9901 and D9902A were combined and analyzed; the authors reported a 33% reduction in the risk of death. D9901A was then amended such that the primary endpoint was overall survival and the time to disease-related pain was eliminated as an outcome measure. The amended trial was renamed D9902B, which enrolled patients from August 2003 though November 2007.

Outcomes differ frequently between study protocols and reports of randomized trials and are often undisclosed. This issue is important in that results can be biased if the changes in outcome were made based on unblinded data obtained from the trial. For example, if multiple outcomes were evaluated, then the false positive (or Type I error) rate may be inflated and a statistically significant association may be identified. Selective reporting of statistically significant outcomes may result in outcome reporting bias. However, changes in outcome measures may be appropriate if new information that is independent of the data from the trial warrants a change — i.e. due to change in scientific relevance or challenging of assumptions made in designing the original trial. If made, these changes and the rationale for the changes should be reflected in the registered study protocols and in the reporting of the trial results. Although the reason for elimination of time to disease-related pain as an outcome measure is not described, the change in outcomes in the IMPACT trial does not appear to have affected the validity of the results.

**Potential modification of effect by post-study treatments**

Imbalances in co-interventions between treatment groups can lead to biased results. The purpose of randomization is to minimize imbalances in baseline prognostic factors between treatment groups. Receipt of co-interventions such as docetaxel prior to enrollment in the trial was relatively balanced between the two groups (15.5% vs. 12.2%). However, after study treatment, patients were allowed to receive additional therapies in a non-randomized fashion. Thus, the interpretation of the sipuleucel-T treatment effect depends on post-treatment risk factors such as after-study interventions, which is true of all trials that involve follow-up measurements. The use of post-study interventions raises questions about what is meant by confounding and how to adjust for confounders. The authors acknowledge that “Statistical approaches to assess the effects of subsequent treatment vary; no consensus exists on how to address the confounding effects.”

Post treatment, 195/341 patients (57.2%) in the sipuleucel-T group and 125/171 patients (50.3%) in the placebo group received docetaxel. The authors argued that docetaxel use did not alter their interpretation concerning the efficacy of sipuleucel-T by censoring for docetaxel use (adjusting for the timing of initiation of docetaxel) and demonstrating the censored survival results were similar to the results for the entire sample. They reported a significant sipuleucel-T treatment effect for their censored results (HR 0.78, 95% CI 0.62-0.98). Their analysis addresses concerns about post-intervention docetaxel use as a confounder. However, the results of this sub-group analysis should be interpreted with caution as balance in baseline variables between the two groups was not assured since the use of docetaxel was not randomized. Nonetheless, the results suggest that there was a trend towards a beneficial effect of docetaxel that was independent of study group assignment.
Questions concerning interactions among the treatments were not addressed. An interaction occurs when the effect of one treatment modifies the effect of the other — i.e. that docetaxel is more or less effective than expected in the presence of sipuleucel-T. However addressing questions about interactions analytically would be very speculative given the lack of randomization of docetaxel use and the small samples involved. Furthermore, interactions between study treatment and non-study treatments seem unlikely given the data presented by the authors.

Crossover of placebo patients to APC8015F

The authors acknowledged that a “crossover” design is unusual for comparing survival as a primary outcome but reminded the readers that the original endpoint was time to disease progression. For obvious reasons, the authors did not analyze their study as a crossover study but rather as a parallel two-group randomized trial. The two treatment arms were complicated because the planned interventions (sipuleucel-T or placebo) were followed by optional post intervention APC8015F salvage therapy available to patients in the placebo condition (63.7%). In addition, patients received other treatments post intervention outside of the study, as described above.

The authors argued that the optional post treatment crossover in the placebo group to APC8015F salvage therapy did not confound their reported sipuleucel-T treatment effect because median survival in the placebo group compared favorably with controls in other RCTs involving similar patient populations. Furthermore, median survival for patients that received APC8015F was 23.8 months compared to 11.6 months for placebo patients that did not receive APC8015F. Had APC8015F adversely affected survival, the reported treatment effect in the placebo group could be explained by the APC8015F salvage therapy. If APC8015F actually improved survival as the non-randomized results suggest, the reported sipuleucel-T treatment effect was actually attenuated. The authors could have compared survival in three groups: sipuleucel-T, placebo with APC8015F, and placebo without APC8015F or by censoring for APC8015F use as they did to compare the effect of docetaxel.

What are the results?

Patients who were randomized to receive sipuleucel-T had a relative risk reduction of 22% of death as compared to those in the placebo group (HR 0.78, 95% CI 0.61-0.98), which corresponded to an increase in median survival of 4.1 months.1 There was no significant difference in time to disease progression. The results of this trial were consistent with results from D9901 and D9902A, which reported an overall 33% reduction in the risk of death and an increase in median survival from 18.9 to 23.2 months.3

Adverse events were reported more frequently in the sipuleucel-T group. Specifically, cerebrovascular events were reported in 2.4% patients in the sipuleucel-T group versus 1.8% in the placebo group. The authors do not report whether the 3 patients in the placebo group who had a cerebrovascular event received APC8015F. Results from the prior two randomized trials also suggested a potential increase in cerebrovascular events with sipuleucel-T, with an incidence of 7.5% versus 2.6%.3 Although the results were not statistically significant, they should be interpreted with caution as most randomized trials lack the sample size and/or duration of follow-up to adequately assess harms.4 In determining whether or not to apply this therapy to individual patients, both the potential benefits and the risks need to be assessed.10

Can the results be applied to patient care?
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Recommendations for interventions depend not only on the quality of the evidence but also about the balance between risks and benefits, individual patients’ values and preferences, and use of resources. The IMPACT trial is the third randomized trial evaluating sipuleucel-T for castration-resistant prostate cancer. In evaluating the quality of the evidence, the results are consistent with those of the prior two trials and the estimates of treatment effect are relatively precise. Although there were limitations in the trial analysis, the authors acknowledged and attempted to address these limitations. In deciding whether or not to use the therapy, potential risks and benefits for individual patients must be determined in terms of (1) quality of life given that disease progression is the same and only survival is extended and (2) risks of harm such as cerebrovascular events which have not been completely assessed. Lastly, it is unclear from the results of this trial whether the magnitude of benefit (and risk) is the same across severity of disease at baseline -- the IMPACT trial differed from the two prior trials in the inclusion of patients with any Gleason score and patients whose disease was minimally symptomatic.

References
Clinical Review by David F. Penson, MD, MPH

Article Reviewed


Review

This article describes the IMPACT study, a randomized clinical trial of 512 men with documented metastatic resistant prostate cancer (mCRPC). The subjects were asymptomatic or minimally symptomatic and had good function status (ECOG functional status 0 or 1). They were randomized in a 2:1 fashion to receive either 3 cycles of sipuleucel-T (Provenge) or placebo. Sipuleucel-T is a form of immunotherapy. For each cycle, the patient undergoes leukapheresis on day 1. His leukapheresis product is then shipped to a manufacturing plant and during days 2 or 3, it is prepared at the plant. The final product, sipuleucel-T, therefore, is made from the patients own cells and cannot be infused into another patient. After manufacturing, on day 4, it is shipped back to the clinician’s office and infused into the patient. While the primary endpoint of the IMPACT study was overall survival, clinical progression was a secondary endpoint. At the time of progression, the patients were unblinded. If a patient that progressed was in the placebo group, he was then offered the opportunity to receive sipuleucel-T made from his previously frozen leukapheresis product (collected as part of the placebo treatment) on a salvage protocol. The IMPACT study showed a statistically significant improvement in survival favoring the sipuleucel-T arm, with a median survival advantage of 4.1 months. Time to progression was similar between the two arms of the study.

Are the results valid?

As a co-author of the study, I need to disclose upfront that I may have some personal bias, as I am convinced that the results are valid and that sipuleucel-T represents a significant advance in the care of men with mCPRC. That being said, there are a number of issues we need to consider regarding the validity of the findings. First, there is the paradoxical finding of a survival advantage in the absence of any effect on disease progression. In theory, progression should be a proxy endpoint for survival and one would not expect to find a survival benefit in the absence of progression. However, consider the hypothesized mechanism of action for sipuleucel-T (the exact mechanism of action is unknown)-Sipuleucel-T is an active immunocellular therapy. This means that the patient’s own antigen presenting cells are activated to create sipuleucel-T and are then reinforced back into the body. In theory, these cells now activate other components of the immune system to combat the cancer. It is likely that this takes a number of months for the full effect to “kick in”. As such, it may be that the disease progresses radiologically while the immune system is being recruited but once the full effect of the sipuleucel-T is reached (after progression), it may still impact the disease course and survival. The supporting evidence for this hypothesis is in the survival curves, which do not diverge until roughly 6 months after randomization. Bear in mind that the study protocol’s first assessment for progression was quite early (6 weeks for CT scan and 10 weeks for bone scan). Obviously, this is somewhat hypothetical, but it certainly has face validity and, given the two endpoints, survival is clearly the more important to patients.

The second issue to consider regarding the validity of the study is the possibility of imbalance between the two arms regarding the use and timing of docetaxel, the only other FDA-approved agent that has
been shown to prolong survival in this setting. To address this issue, the authors generated an additional proportional hazards model that specifically controlled for both the use and timing of docetaxel. The relative risk ratio was remarkably similar to the primary analysis (RR=0.78, p=0.03). While not a perfect solution (a better but unethical approach would have been to restrict the analysis to docetaxel-naïve patients and restrict docetaxel use after enrollment as well), this is a valid way to deal with this issue.

While there have been a number of other criticisms of the study (comparability of the study population to those enrolled in the definitive TAX327 study, which the FDA used to approve docetaxel in this setting, as an example), most are unfounded or do not really influence the validity of the results. In summary, the findings likely are valid and have been recapitulated in two smaller studies of sipuleucel-T.

What are the results?

For the most part, these were discussed earlier but there are three other points regarding the results which may be useful when counseling patients. First, sipuleucel-T is not a curative treatment. It prolongs survival, but the vast majority of men in the study still died of prostate cancer. Second, while survival is prolonged, this is still a disease that moves fairly quickly. The estimated probability of survival 36 months after randomization was 31.7% in the sipuleucel-T group and 23.0% in the placebo group. Finally, while it is inappropriate to compare survival in the treatment arm of this study to the treatment arm of patients in TAX327, it is reasonable to state that sipuleucel-T is considerably less toxic than docetaxel and the course of therapy is much shorter.

Can the results of this study be applied to patient care?

The short answer to the question is yes. The longer answer is much more complicated. First of all, the study only focused on men with good functional status with asymptomatic or minimally symptomatic mCRPC. These results cannot (and should not) be applied to men with earlier stage disease. Furthermore, because the survival curves do not diverge until roughly 6 months after randomization, this agent should be reserved for men who have a life expectancy of approximately one year or more. All that being said, we currently treat these patients with docetaxel or secondary hormonal manipulation. Clearly, given the favorable side effect profile, many of these patients will now opt for sipuleucel-T.

The other issue regarding patient care centers on treatment cost. It is public knowledge that this agent costs $93,000 for the three cycles. ($31,000 per cycle). One might question whether a median 4-month survival benefit justifies the cost of therapy. This is a difficult question to answer and raises a myriad of issues that go beyond just sipuleucel-T in mCRPC. Before you jump to any conclusions regarding this perplexing question, I would remind you that many of our interventions in medicine in general and urology specifically may not pass muster if we view them through the lens of cost-effectiveness. That being said, I completely understand and share the concern over the upfront high cost of sipuleucel-T. In my practice, I explain the situation to the patient and remind them that they may be responsible for a significant portion of the treatment, as the payors who are covering the agent (and not all are) are often asking patients to bear a 20% copayment. Since the patient is the one with the terminal disease, I think it is better for him to decide what a 4-month median survival is worth to him.