Putting Provenge in Perspective

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As a clinician and researcher in the prostate cancer field, I have been hearing that prostate cancer is “20 years behind” breast cancer now for the last 25 years! Who would have thought that poor ol’ prostate cancer would have an FDA-approved immunotherapy before breast cancer—and in fact, before any cancer!? [1] Furthermore, as a urologist, I am proud that a urologist is at the heart and soul of this advance, serving as the CEO of Dendreon, the company that has developed and commercialized sipuleucel-T (Provenge). Much has been written about sipuleucel-T over the last decade—and particularly over the last several years, since it was initially rebuffed by the FDA and then approved in May 2010. [2-5] Drs. Garcia and Dreicer have done an outstanding job of describing the development of sipuleucel-T, the other vaccines/immunotherapy approaches that have been developed for use in advanced prostate cancer, and the phase III results of the pivotal IMPACT trial that resulted in FDA approval for sipuleucel-T.

Putting the sipuleucel-T FDA approval in the context of other new drug approvals of this past year yields a picture that is just as remarkable as the novel immunotherapy itself. After the approval of docetaxel (Taxotere) in 2004, the prostate cancer field went through a “dry spell,” with only one other agent approved between 2004 and 2010. Although degarelix (Firmagon), a pure gonadotropin-releasing hormone (GNRH) antagonist was approved by the FDA in December 2008, [6] it was 6 years after the approval of docetaxel before there was another new agent. Then in 2010, the field exploded, with sipuleucel-T approved in May, cabazitaxel (Jevtana) in June, and denosumab (Xjeva) in November. [7, 8] In addition, we learned in 2010 that bevacizumab (Avastin) added to docetaxel did not extend survival compared with docetaxel alone in castration-resistant prostate cancer (CRPC). [8] We also learned that the novel endothelin antagonist ZD-4054 (zibotentan) did not improve survival compared with placebo in castration-resistant prostate cancer (CRPC). [9] On the other hand, we learned that abiraterone, a novel oral androgen synthesis lyase inhibitor, prolonged survival in men in whom docetaxel had failed, with speculation rising that the FDA would approve abiraterone in 2011. [10] All this is amazing considering that the realm of therapeutics in CRPC had been quiescent for the last 6 years! Much has been written about the 4.1-month survival benefit of sipuleucel-T compared to placebo in men with asymptomatic or minimally symptomatic CRPC, and the relationship between this benefit and the lack of a symptomatic or prostate-specific antigen (PSA) response to the therapy. In other words, there was no difference in time to progression between the two arms in the D9901 or the IMPACT phase III randomized controlled trials; however, both trials showed the 4-month overall survival benefit. Furthermore, much has been written about how the $93,000 wholesale cost of the 3-infusion sipuleucel-T treatment stacks up against the clinical benefit. While some maintain that the cost seems “high” given the limited duration of therapy, others have contended that the cost per year of life saved is in line with the costs of other modern novel cancer therapies. A full-scale discussion of the socioeconomic implications of sipuleucel-T is not possible here; suffice it to say that cost-benefit issues have been raised by this novel, first-in-class immunotherapy.

Considering the growing “toolbox” of therapies for CRPC, I would like to emphasize where sipuleucel-T “fits” in the sequence of agents used to treat advanced prostate cancer. The inclusion criteria of the IMPACT trial were:

• Histologically documented adenocarcinoma of the prostate.
• Metastatic disease as evidenced by soft tissue and/or bony metastases.
• CRPC: current or historical evidence of disease progression concomitant with surgical or medical castration as demonstrated by PSA progression OR progression of measurable disease OR progression from nonmeasurable disease.
• Serum PSA level ≥ 5.0 ng/mL.
• Castrate levels of testosterone (< 50 ng/mL).
• Life expectancy of at least 6 months.
• Age ≥18 years.
• Adequate hematologic, renal, and liver function
• Negative results on serology tests for HIV-1 and HIV-2, human T-cell lymphotrophic virus (HTLV)-1, and hepatitis B and C.

The exclusion criteria for the trial were:
• Presence of lung, liver, or known brain metastases; malignant pleural effusions; or malignant ascites.
• Moderate or severe symptomatic metastatic disease.
• Significant pain, as established by either of the following:
  - A requirement for treatment with opioid analgesics for any reason within the 21 days prior to registration.
  - Average weekly pain score of 4 or more as reported on the 10-point Visual Analog Scale on the registration pain log.
• Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2.
• Use of nonsteroidal antiandrogens within 6 weeks of registration.
• Treatment with chemotherapy within 6 months of registration; treatment with chemotherapy within ≥ 3 months was allowed if all the following criteria were met:
  - Post-chemotherapy PSA was ≥ pre-chemotherapy PSA or ≥ nadir PSA achieved during chemotherapy.
  - Post-chemotherapy bone scan was not improved compared with pre-chemotherapy bone scan.
  - For patients with nodal disease, post-chemotherapy imaging did not show a decrease in the size or number of pathologically enlarged lymph nodes compared with pre-chemotherapy imaging study.
• Two or more chemotherapy regimens prior to registration.
• Initiation or discontinuation of bisphosphonate therapy within the 28 days prior to registration.
• Treatment with any of the following within 28 days of registration:
  - Systemic corticosteroids.
  - External beam radiation therapy or surgery.
  - The herbal supplements PC-SPES or saw palmetto.
  - Megestrol acetate, diethylstilbestrol, or cyproterone acetate.
  - Ketoconazole.
  - 5-α-reductase inhibitors.
  - High-dose (> 7.0 μg/wk) calcitriol.
  - Any other systemic therapy for prostate cancer.

The reason I have listed these criteria is that sipuleucel-T is a novel therapy that is currently in limited supply; thus, it is prudent to follow guidelines for identifying which patients are optimal candidates. In general, this therapy is for men who are in the early stage of CRPC, who have not yet received systemic chemotherapy, and who do not yet have pain requiring narcotics. Because this is an immunotherapy, we prefer patients with a robust immune system, and we want men who we feel will have stable disease for several months after the therapy to allow the immunity to develop.

A typical case might be the following:
• A man 69 years of age.
• History of radical prostatectomy.
• Luteinizing hormone-releasing hormone (LHRH) agonist monotherapy post-surgery for PSA/biochemical recurrence.
• After 15 months, progressive rise in PSA level.
• No effect of additional anti-androgen on serum PSA level.
• PSA level continued to rise.
• Nilutamide (Nilandron) used, followed by ketoconazole/prednisone.
• PSA level continued to rise.
• Patient is asymptomatic but with evidence of bony metastases in spine.

This man has asymptomatic castrate-resistant or hormone-refractory prostate cancer, and he meets the on-label indication for sipuleucel-T therapy.

In summary, Drs. Garcia and Dreicer have provided a very nice overview of immunotherapy in CRPC and of the place of sipuleucel-T in the treatment of our patients.

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References:


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