Sipuleucel-T (Provenge®) - autopsy of an innovative paradigm change in cancer treatment: Why a single-product biotech company failed to capitalize on its breakthrough invention.

Running Head: Sipuleucel-T (Provenge®) – why a single-product company failed to capitalize on its breakthrough

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Abstract

Approved by the Food and Drug Administration (FDA) in 2010, sipuleucel-T was the first "personalised" cancer vaccine to treat prostate cancer in the metastatic, non-symptomatic population of 30,000 men in the US. Sipuleucel-T is prepared individually for each patient and infused in three sessions over one-month. However, in 2015, sipuleucel-T's owner, Dendreon, filed for bankruptcy. This opinion paper reviews the probable reasons why this innovative product failed to achieve commercial success. We performed PubMed and internet searches focused on pricing, reimbursement and market access. We found that sipuleucel-T's FDA approval was delayed by 3 years, reportedly because of the vaccine's new mechanism of action. Sipuleucel-T was cleared by the European Medicines Agency two years later, but other national agencies were not approached. It was priced at $US93,000 for a course of treatment. This high price combined with the company's late securement of reimbursement for the vaccine by the US Centers for Medicare & Medicaid Services (CMS) resulted in another year's delay in accessing the market. In spite of a positive recommendation by the National Comprehensive Cancer Network, sipuleucel-T's complex administration, high price and uncertainty about the reimbursement status deterred doctors from the product. Further, the vaccine's supply was limited during the first year of launch, due to a small manufacturing capacity. Two oral metastatic prostate cancer drugs with similar survival benefits reached the US market one and two years after sipuleucel-T. And even though Dendreon's market capitalization topped $US7.5 billion following FDA's approval of sipuleucel-T, this value degraded gradually until the firm's bankruptcy five years later. We conclude that the bankruptcy of Dendreon was largely due to the delay in securing FDA approval and CMS coverage, as well as the high cost that had to be incurred by providers up-front. Licensing sipuleucel-T to a Pharmaceutical company more experienced in the market access pathway may have saved the company and the product.

Key Points:

- Approved in the US in 2010, sipuleucel-T was the first therapeutic vaccine to treat cancer, first alternative to chemotherapy for metastatic prostate cancer patients with few side effects and first biological and personalised treatment for prostate cancer.
- In spite of being acclaimed as a paradigm shift in cancer treatment, the product had a consistently disappointing sales record and the company behind the vaccine went into bankruptcy five years after the product's launch.
- Poor market access experience of the single-product biotech company implies it may have benefited from a partnership with or outsourcing to a more experienced Pharmaceutical company, in order to capitalise on their invention

Background

Prostate cancer is the most common cancer in men in the United States (US), after skin cancer. It is estimated that, in 2015, 220,800 men will be newly diagnosed with prostate cancer in the US, and about 27,540 men will die of the disease. The 5-year relative survival rate for men diagnosed from 2001 to 2007 with local or regional disease was 100%, and the rate for distant disease was 28.7%; a 99% survival rate was observed for all stages combined. In 2012, there were an estimated 2,795,592 men living with prostate cancer in the US [1, 2].

Standard treatments for prostate cancer in the US include watchful waiting, surgery, radiation therapy, hormone therapy, chemotherapy, and bisphosphonate therapy. Because of the high efficacy of standard treatments in patients with early disease, newer treatments targeted the more advanced metastatic cancer stages. They include the intravenous therapeutic vaccine sipuleucel-T (Provenge®) introduced in the US in May 2010 for asymptomatic patients with metastatic, castration-resistant prostate cancer (mCRPC) prior to chemotherapy, and two non-biological oral agents; abiraterone (Zytiga®) introduced in April 2011 for the same population (initially for post-chemotherapy but later extended to the pre-chemotherapy population in December 2012) and enzalutamide (Xtandi®) approved for the chemotherapy-naive population in August 2012.

This opinion paper reviews probable causes of why this innovative product failed to achieve commercial success in the US and Europe. Five years after its launch in the US, the company behind the vaccine, Dendreon, filed for bankrupcy and was aquired by a larger pharmaceutical company. While the drug is still offered in the US, it was withdrawn from the European market for commercial reasons, merely a few months after obtaining its European marketing authorization.

Search strategy

We performed a literature research to inform this opinion paper. Inclusion criteria were defined as any literature on sipuleucel-T that would reflect the clinical, healthcare management, market access, pricing, health technology assessment and business points of view in both US and European markets. We performed a Pubmed search using the query (reimbursement OR coverage OR payment OR payers OR cost OR price OR pricing OR cost-effectiveness OR Medicare OR CMS) AND (provenge OR sipuleucel-T) on the 1st of June 2015. We used the same query on Google to search all websites from the 1st of January 2000. Pubmed and Google searches resulted in 41 and 21,700 hits, respectively. Abstracts of all Pubmed hits and titles of the first 200 Google hits were screened by one author for relevance. Further, the following Pharma websites were searched with the query (provenge OR Sipuleucel-T) or its equivalent (number of hits): www.pharmatimes.com (31), www.fiercepharma.com (474), www.xconomy.com (211), www.pmlive.com (45), http://www.biocentury.com (275), http://www.scripintelligence.com (146, for "provenge"). These results were screened for complementary information.

Approvals and licensing

While the three novel treatments (sipuleucel-T, abiraterone and enzalutamide) for mCRPC showed a similar survival benefit of about 4 months in randomised clinical trials versus placebo, sipuleucel-T reached the market first and was revolutionary on many levels [3]. It was the first therapeutic vaccine to treat cancer, first alternative to chemotherapy in this population with few side effects, first biological treatment and first personalised treatment for prostate cancer [3].

Sipuleucel-T is prepared individually for each patient by harvesting their dendritic cells (antigen-presenting cells) in a procedure called leukapharesis [4]. The cells are then taken to a manufacturing

plant and mixed with a proprietary fusion protein (PA2024) that contains the PAP antigen, which is quite abundant in prostate cancer cells, which then primes the cells to recognize and attack the tumour. The activated blood product is returned to the infusion center and re-infused into the patient to cause an immune response against cancer cells carrying the antigen.

The US Food and Drug Administration (FDA) rejected Dendreon's first application for the drug in May 2007 [5]. According to the agency their two phase III trials, in which the vaccine was compared with placebo, failed to achieve the primary endpoint, based on the trial design, which was progression-free survival. This is because advanced-stage cancer treatments do not typically extend survival, but merely stop the tumour progression. Sipuleucel-T however, had the opposite effect of extended survival, with no measurable tumour shrinkage.

However, the medicine was approved three years later based on data from an extra clinical trial versus placebo which the FDA had requested. The new trial largely repeated previous findings in terms of a survival gain of about 4 months versus placebo (25.8 months versus 21.7 months) and no improvement in progression-free survival. Sipuleucel-T was licensed by the FDA in 2010 for the treatment of asymptomatic or minimally symptomatic mCRPC [4]. The FDA requested a 1500-patient registry to assess the risk of stroke in people on sipuleucel-T. Other outcomes to be collected were marked as commercial in confidence [5].

Dendreon applied for the authorisation at the European Medicines Agency (EMA) in December 2011 and obtained the license almost two years later in September 2013 [6]. The license was slightly narrowed, as compared to the US license, to patients with non-visceral metastases and who have not yet received chemotherapy. The EMA requested further post-marketing studies, addressing safety concerns related to embolic and thrombotic events, cerebrovascular events, infections and the quality of the vaccine produced in the European plant.

But sipuleucel-T was only launched in the UK and German markets in March 2014, which is when Dendreon's contract manufacturing organization, PharmaCell was ready to prepare samples for the local patients [7]. The company did not acquire the license for sipuleucel-T outside the US and Europe.

It is noteworthy that a month after obtaining FDA approval, sipuleucel-T also received a strong recommendation for its on-label use by the National Comprehensive Cancer Network [8]. The authoritative European Society for Medical Oncology (http://www.esmo.org) did not publish prostate cancer guidelines after sipuleucel-T was launched in Europe and so, the vaccine could not be endorsed by them.

Price and Reimbursement decisions

For Dendreon's US investors, FDA approval was the first step toward realising returns on the invention that consumed 15 years and $US1 billion to finally reach the market [9, 10]. A price tag of $93,000 for a course of three infusions was higher than any of the analysts had speculated in the preceding weeks [11]. The company estimated the total potential US market for sipuleucel-T at 30,000 patients, or $2.8 billion in annual sales potential [11]. Apart from the obligation to recoup the investment, Dendreon backed its pricing decision by benchmarking prices of other oncology drugs used in terminally ill patients [11]. The company argued, based on market and payers research, that payers were willing to pay $23,000 per extra month of life in this group of patients. With an average survival gain of 4 months on sipuleucel-T vs. placebo, this amounted to $92,000 – nearly the price of a full course of treatment [10]. Further, Dendreon believed that because of fewer side effects with sipuleucel-T as compared to chemotherapy, supportive care costs for patients were reduced [10].

However, these were not comprehensive cost-effectiveness analyses. A number of articles in medical and health care management journals predicted the high price may limit sipuleucel-T's adoption or put extraordinary strain on public, individual and insurer's budgets [12-17]. $US272,000 per additional year survival was considered far above acceptable levels at that time in the US or Europe [18, 19].

However, in the US, formal cost-effectiveness is not mandatory to obtain payer approval. Moreover, in the case of the government payer Medicare, the cost of medicine should not be a factor when making coverage decisions. Nevertheless, on 30 June 2010 the US health care financing agency, Centers for Medicare & Medicaid Services (CMS), launched a formal inquiry, called a National Coverage Determination (NCD), to decide whether sipuleucel-T was a "reasonable and necessary" treatment and thus should be reimbursed nationally [20-22]. The NCD is a 12-month long process which includes a technology assessment (TA) reviewing treatment outcomes and side effects, but not cost-effectiveness.

The final TA report by the US Agency for Healthcare Research and Quality (AHRQ) stated that the three randomized clinical trials provided "consistent evidence" that sipuleucel-T prolonged survival, however, due to confounding study design, the quality of evidence was judged as "fair" [22].

On November 17 2010, when rating the quality of evidence supporting sipuleucel-T, many committee members felt that coverage should be conditional on the submission of new evidence in a process called Coverage with Evidence Development (CED) [22, 23]. However, the final NCD in June 2011 did not deem CED necessary for on-label use, as the efficacy data was sufficient. This paved the way for seamless reimbursement of sipuleucel-T by CMS providers across the country.

In terms of cost-effectiveness, a study on sipuleucel-T published in 2014 concluded it was not cost-effective from the US societal perspective, compared with prednisone in the treatment of asymptomatic, pre-docetaxel mCRPC [24]. Similarly, Health Technology Assessments (HTA) from authorities in the two European countries where sipuleucel-T was marketed were also sceptical about the vaccine's value-for-money. In March 2015 Germany's Institute for Quality and Efficiency in Health Care (IQWiG) concluded there was "non-quantifiable" benefit compared with androgen deprivation therapy [25]. In February 2015 the UK's National Institute for Health and Care Excellence (NICE) decided not to recommend the vaccine for use on the National Health Service (NHS) due to lack of cost-effectiveness compared with the new oral agent abiraterone acetate or best supportive care [26].

Political pressure

The head of the Coverage and Analysis Group at the CMS said there had been political pressure on the agency to make the drug fully available throughout Medicare: "While the cost of Provenge was not an issue in our coverage determination, I think it is fair to say that the cost of Provenge created a public buzz around this particular product, which then made it a higher-profile issue and something that we should look at." [21]

As the Medicare Evidence Development and Coverage Advisory Committee voting was approaching on 17 November 2010, sipuleucel-T's advocates in the Congress inquired to the CMS about alleged unfair treatment of the drug by the agency, to which the head of the Coverage and Analysis Group replied by pointing out that, quick action on the NCD was justified because "the FDA had noted the stroke risk in the label, and also because Provenge failed its two trials." But all other accusations were rebutted [21].

Logistics and supply of sipuleucel-T

Dendreon's manufacturing capacity remained low for over a year after sipuleucel-T's launch [10]. This was because the company did not raise suitable funds until after receiving FDA approval. Thus, only one in 10 patients eligible for the vaccine could be treated in this period [10, 27] and there were only 50 infuser accounts located in the academic sites which ran its clinical trial [10, 27].

Faced with the vaccine's scarcity, one academic centre even developed a rationing policy to ensure greater equity in patient's access to the treatment [28].In March 2011 Dendreon finally expanded its manufacturing capacity and opened new infuser accounts [29].

Reimbursement issues faced by providers

Prostate cancer is a disease that mostly affects men over 65 for whom Medicare covers 80% of medical expenditure. Whereas the 50 academic sites were used to handling the somewhat complex delivery and reimbursement of innovative cancer therapies, local Medicare providers, did not receive sufficient support from Dendreon in handling the reimbursement of the drug [16]. For example, as the drug represented a novel therapeutic class and targeted a specific population of mCRPC patients novel administrative codes were needed to streamline the reimbursement process. A lack of such codes was likely causing confusion with reimbursement at local provider level and compromising doctors ability to identify patients eligible for the treatment [16].

Non-academic providers, who were confronted with early demand for the drug, were understandably reluctant to authorize the large up-front expenditure involved. They reportedly flooded Medicare with complaints about the high cost and uncertain clinical benefit of sipuleucel-T [21]. They were also confused about the classification of sipuleucel-T as a vaccine, as Medicare typically does not cover this kind of intervention [21]. Some providers refused to cover sipuleucel-T, while others put restrictions on the licensed indication.

In a delayed response to these challenges, in March 2011 Dendreon ensured that sipuleucel-T's distributor allowed 120 days credit to doctors so that they could address reimbursement claims before needing to pay [29].

Cost and drug administration issues

Two surveys published in late August 2011 revealed both high price and complex administration were significant issues, particularly when patients had to pay for 20% of the cost [30, 31]. Furthermore, the US payers determined the true cost of sipuleucel-T ranged from $100,000 to $120,000, including infusion charges.

Similarly, a 2010 survey of UK oncologists revealed not more than 3% would use sipuleucel-T because of its cost and complexity of administration [32].

Another concern by US oncologists was that sipuleucel-T was lacking a predictive test and markers of efficacy [33].

A clinician who participated in sipuleucel-T's trial said "most patients who received sipuleucel-T eventually received chemotherapy as well. The problem is that you wind up paying for more treatment later" [23].

In a survey of private payers in June 2010, 46 percent responded that they would not pay without patients first undergoing chemotherapy [21] even though sipuleucel-T was approved by the FDA as a pre-chemotherapy treatment.

Arrival of competitors

While Dendreon experienced a significant delay obtaining FDA approval other companies had future competitors in their pipelines. Indeed, in April 2011 (four years from Dendreon's first FDA application) a new mCRPC drug, abiraterone, reached the US market [3, 34]. Initially approved for use after chemotherapy, it obtained pre-chemotherapy approval in December 2012. Another mCRPC drug, enzalutamide, received FDA approval in August 2012 [34]. Abiraterone and enzalutamide showed similar survival gains to sipuleucel-T in clinical trials, however, while both abiraterone and enzalutamide were administered orally, sipuleucel-T was administered intravenously in three complex sessions [34]. Furthermore, the vaccine was the second most-expensive treatment [35].

Financial problems of Dendreon

Despite the positive reimbursement decision by the CMS, sales of the vaccine stagnated. On 3 August 2011 Dendreon withdrew its optimistic revenue forecast of $US350-400 million for 2011 [36]. This news cut the company's market capitalization by two-thirds.

Soon after, in September 2011 Dendreon's CEO departed along with 25% of the company's staff (500 people laid off) dictated by a need to cut operating costs [37].

In July 2012, as sales of sipuleucel-T continued to disappoint, Dendreon's new CEO decided to cut another 600 jobs and close one of its three manufacturing sites, while increasing output at the remaining sites, hoping to save $US150 million over the next 12 months [38].

Sales from the year 2012 amounted to $US325.3 million, up from $US213.5 million for 2011, but still much below the $US350-400 million the former CEO had promised. However, sipuleucel-T's sales declined in the quarter immediately following abiraterone's approval in the pre-chemotherapy setting in December 2012. The company continued to experience losses throughout 2013, in spite of obtaining EU approval in June 2013 [39].

The new CEO saw the "high cost of sales" as the major cause of Dendreon's losses and aimed at reducing it from 53% to mid-30% range. Indeed, the costs seemed steep compared with an average in the biotech industry of about 10%. By November 2013, Dendreon announced further layoffs of 150 people, as a result of improved automation in its manufacturing plant. Analysts saw the cost-cutting efforts as preparation for the sale of the company.

Despite these efforts Dendreon recorded $620 million in convertible debt due in 2016, and yet another CEO had to step down. The firm filed for bankruptcy in November 2014. It was acquired for $495m by Valeant in March 2015 with a view of maintaining the vaccine in the US market. Following the takeover, the new owner announced further layoffs of Dendreon's staff. On 6 May 2015, Valeant requested the withdrawal of the EMA'S sipuleucel-T authorization in Europe for commercial reasons [40].

Conclusions

Dendreon's pioneering experience with the FDA paved the way for potential future therapeutic cancer vaccines. A change of paradigm from delaying tumour progression to extending survival should inform the design of future clinical trials for cancer vaccines. However, repeating this

observation with other vaccines and explaining the elusive mechanism of action remain a challenge. Further, a survival benefit in advanced cancer patients greater than just a few months is an outcome much awaited by the oncologists and cancer patients [41, 42].

Even though Dendreon's market capitalization topped $US7.5 billion following FDA approval, this value eroded gradually until the firm's bankruptcy five years later. Dendron's bankruptcy was multi-factorial, of which two issues contributed the most: the delay in securing FDA approval and CMS coverage and the very high price that had to be incurred by providers up-front. In practice, the product was characterised by many potential barriers to market access such as; a mechanism of action previously unknown to the FDA, EMA or CMS, high up-front costs, complex administration, limited manufacturing capacity, no markers of treatment response and soon-to-arrive competitor drugs.

Possibly, a company with a greater experience or supported by a strong regulatory and market access advisory partner would have cleared the FDA and CMS hurdles sooner and would have engaged in early dialogue with providers facing issues with high cost and complex administration. Also, Dendreon's inability to raise funds to upscale manufacturing capacity, establish more infusion centres and promote the vaccine until after FDA approval translated into another year of delay. The confusion around CMS reimbursement status, combined with acute scarcity of the vaccine resulted in doctors and payers forming a negative image of the product. That period was also a missed opportunity to expand beyond the US to locations such as Japan, South America, Europe, etc.

Once competitor drugs with similar survival benefit, a possibility of monitoring treatment response, simpler route of administration and lower up-front costs arrived, it became increasingly difficult to gain a substantial share in the market. Dendreon's lack of a major pharmaceutical partner meant it simply did not have the marketing muscle to compete against the industry giants Johnson & Johnson (abiraterone) or Medivation (enzalutamide) which partnered with the second largest Japanese pharmaceutical company, Astellas Pharma.

The oncology market is becoming increasingly competitive and payers' expectations from new treatments are even higher survival gains at reasonable prices. Therefore, small biotechnology firms paving the way for dramatic paradigm shifts should carefully manage risk by licensing their products to, or partnering with larger companies, that have suitable experience and finance. Dendreon is an example that illustrates the difficulty for small biotechnology firms to address complex multiple challenges including leading a change in paradigm.

Compliance with Ethical Standards

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