Velcade®, New Science and New Hope: A Case Study

Multiple myeloma (or myeloma) is cancer of plasma cells, which are blood cells produced in the bone marrow that fight infection in the body. The cancerous plasma cells accumulate in the bone marrow, where they suppress normal marrow function, so that blood lacks the normal plasma cells needed to fight infection. Additionally, the cancerous cells form tumors that cause dangerous bone thinning. Excess blood calcium from dissolving bone often damages the kidneys. The cause of myeloma is not known, and, currently, there is no cure.

Velcade® (bortezomib), developed by Millennium Pharmaceuticals, Inc., is a medical breakthrough. It is the first myeloma treatment approved by the Food and Drug Administration (FDA) in over a decade. Patients who do not respond to other therapies have high response rates to Velcade® -- giving extra months of life to patients for whom no other therapy is effective. Results from early clinical testing were so optimistic that the FDA granted Velcade® accelerated approval before data from controlled studies were available.

Velcade® is also a scientific breakthrough -- a completely new approach to treating cancer. Velcade® inhibits the activity of the proteasome, an enzyme complex that regulates many routine cell activities necessary for cell reproduction and survival. The proteasome also promotes the creation of proteins that resist cell death. By reducing proteasome activity, Velcade® disrupts the normal maintenance of cell functions and reduces the ability of the cell to resist attack, resulting in cell death. Velcade is the first FDA-approved drug to target the proteasome.

Epidemiological Features of Myeloma

Myeloma is the second most prevalent blood cancer, after non-Hodgkin's lymphoma. It accounts for roughly 1% of all cancers and 2% of all cancer deaths.[i]

Epidemiologic Measure	Statistics
Annual New Cases / Deaths	14,600 / 10,900[ii]
Age-adjusted Incidence	5.6 / 100,000 [iii]
Median Age at Diagnosis	71[iv]

Management of Myeloma

Patients in the early stage of myeloma often have no symptoms, and may remain stable for months or years. These patients are monitored, but not treated. Over time, cancerous cells slowly accumulate in the bone marrow and the blood concentration of normal cells decreases. If a patient exhibits symptoms while the myeloma is still stable, they may be treated and the frequency of monitoring may be increased.

Most often, however, myeloma is not discovered until it reaches an advanced or "progressive" stage. Patients with progressive myeloma usually have multiple bone tumors, anemia, significant blood abnormalities and kidney impairment. These patients receive immediate treatment for myeloma.

Chemotherapy is the mainstay of first-line treatment of progressive myeloma. A variety of drugs and drug combinations have been shown to prolong the life of myeloma patients, however, there is no consensus on the best first-line chemotherapy.

It is uncommon that patients experience long complete remissions of myeloma after first-line therapy. Appropriate second-line therapy depends on how the patient responded to the first treatment. A new choice from the menu of chemotherapy options may be administered, or the patient may undergo an autologous stem cell transplant. Unfortunately, patients eventually relapse after second-line therapy, and additional treatments are necessary. Velcade® provides a much needed treatment option for these patients.

Velcade® is indicated for the treatment of myeloma patients who have received at least two prior therapies and whose disease progressed following the last therapy. The anti-myeloma effects appear to stem not only from direct effects on myeloma cells, but also from effects on bone marrow conditions that help sustain tumor growth.

Development of Velcade®

Role of NIH

The National Cancer Institute (NCI) of the National Institutes of Health (NIH) has unique resources for the development of compounds with therapeutic potential including the Cancer Therapy Evaluation Program (CTEP) that sponsors clinical trials to evaluate new anti-cancer agents. The particular emphasis of the program is

R&D TIMELINE

Myogenetics creates proteasome inhibitors (PI) ***mid 1990s***

Myogenetics explored disease applications for PIs ***1994-1996***

MG-341 (Velcade Precursor) synthesized ***1995***

Myogenetics renamed ProScript and MG-341 renamed PS-341 ***1995***

Cytotoxic profile of PS-341 discovered ***1995-1997***

CRADA between ProScript and NCI signed ***1998***

ProScript filed IND with FDA ***1998***

to elucidate molecular targets and mechanisms of drug effects. In 1998, Proscript Inc. and NCI entered into a Cooperative Research and Development Agreement (CRADA) to utilize the expertise and clinical trials networks of CTEP to study ProScript's promising anti-cancer chemical compounds. The key outcome of the CRADA collaboration was that Dr. Shanker Gupta at the NCI discovered how to protect these boronic compounds by creating a freeze-dry powder formulation. This dry formulation remains effective while exhibiting a dramatically longer and stable shelf life.

NCI carried out multiple clinical trials under the CRADA using its clinical trial networks. These data was crucial for understanding the therapeutic activity of Velcade® and its potential use to treat various cancers, although the data from these studies were not used to gain FDA approval. The FDA also designated Velcade as an Orphan Drug due to the rare occurrence of myeloma.

The NIH Office of Technology Transfer exclusively licensed Dr Gupta's discovery to an industrial partner to provide an incentive for investment for the continued development of Velcade®. This license also included a commercial development plan to maximize likelihood of producing a drug.

Role of Private Partner and its Collaborators[v]

During the mid 1990s a team of scientists at Myogenetics created a group of proteasome inhibitors to block protein degradation in wasting syndrome. They then explored the application of proteasome inhibition in other diseases including rheumatoid arthritis, asthma and cancer. The active ingredient for Velcade, a proteasome inhibitor, was first synthesized by Myogenetics in 1995.

In that same year, Myogenetics was renamed ProScript, and the company continued studies with this active ingredient by conducting extensive preclinical oncology studies. Some of these studies were carried out in collaboration with other institutions. This collaborative research included studying the active ingredient in tumor cells lines with NCI, and its effect in multiple animal cancer models with the Dana Farber Institute.

The first clinical trials were begun by ProScript in 1998 and continued through 2002 in spite of the company being sold twice. In 1999, the current provider of Velcade®, Millennium Pharmaceuticals, collaborated with Dana-Farber Cancer Institute to study Velcade® in multiple myeloma patients after the University of North Carolina achieved a complete response with the compound in the first multiple myeloma patient. That same year, Millennium Pharmaceuticals initiated what would become the seminal clinical trials that resulted in FDA approval to provide Velcade® as a treatment for refractory multiple myeloma.

Currently, Millennium Pharmaceuticals is jointly engaged with Ortho Biotech Products in a comprehensive global clinical development program to investigate the potential of Velcade® to treat different forms of cancer.

In addition, Millennium Pharmaceuticals made the extensive investment necessary to bring Velcade® to market just four and a half years after the treating the first human patient. This remarkable speed stems from the company's willingness to commit enormous resources to drug development, and its early collaboration with the NIH and FDA.

Public Health Benefits

Velcade® provides a new therapeutic for patients who have exhausted available treatment options. Laboratory tests show that Velcade® is effective against cancer cells that have developed resistance to common anti-cancer drugs, and markedly enhances the cell killing effects of chemotherapy agents and of ionizing radiation.[vi] The apparent ability of Velcade® to reverse cancer cell resistance to chemotherapeutic agents is generating excitement and spurring additional new research into potential combinational chemotherapy modalities directed against a variety of cancers. In the clinic, Velcade® is now being tested against ovarian, colon, pancreatic, lung, and prostate cancers, as well as leukemia and non-Hodgkin's lymphoma. Although this drug is presently extending the lives of myeloma patients, the expectant future for Velcade® in treating other cancer patients is great.

R&D Timeline

Clinical trials initiated *1998*

Several key Millennium patents issued *1998 –2004*

Millennium files New Drug Application for Velcade *2002*

License signed *2002*

NIH patent issues *2004*

FDA approval *2003*

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[i] "About Myeloma, Introduction to Myeloma, Causes and incidence," Multiple Myeloma Research Foundation, www.multiplemyeloma.org. Accessed September, 2003.

[ii] Cancer Facts and Figures 2003, p. 4, American Cancer Society.

[iii] SEER Cancer Statistics Review 1975 - 2000, Table I-4.

[iv] SEER Cancer Statistics Review 1975 - 2000, Table I-12.

[v] Personal communication with Millennium Pharmaceuticals Global Affairs representative 7/29/2004

[vi] Mitchell, BS "The Proteasome – An Emerging Therapeutic Target in Cancer," NEJM 348;26, June 26, 2003, pp. 2597 -8.

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NIH Office of Technology Transfer
6011 Executive Blvd. Suite 325
Rockville, MD 20852
U.S.A.