Fludara™ The New Benchmark: A Case Study

For decades, the only treatments for B-Cell Chronic Lymphocytic Leukemia (CLL) were based on alkylating agents. There were no options for patients whose disease did not respond to these drugs. Fludara™ (fludarabine phosphate) was a major breakthrough. It produces high rates of remission, even in patients who do not respond to traditional therapy.

Fludara™ was the first treatment in a new class of highly effective chemotherapy agents (the purine analogues) for CLL. It is related to a known antiviral agent, and influences several enzyme pathways; its precise mechanisms of action are not fully understood. For example, Fludara™ inhibits DNA repair and may also work by blocking the ability of RNA to make proteins.

Today, Fludara™, manufactured by Berlex Laboratories, [i] is among the established first-line therapies for CLL, either alone or as the cornerstone of combination therapy. As researchers continue to investigate new treatments for CLL, Fludara™ is the benchmark against which new therapies are measured.

Epidemiological Features of CLL

Epidemiologic Measure	Statistics
Annual New Cases / Deaths	7300 / 4400 [ii]
Age-adjusted Incidence	3.5/100,000[iii]
Median Age at Diagnosis	72[iv]

Management of CLL

CLL develops in the bone marrow, usually in persons over 50 years old. The cause is not known, and there is no cure. CLL develops slowly, as cancerous cells multiply in the blood and lymph nodes. Patients in the early stages of this disease often have no symptoms and can remain without symptoms for a long time. The typical approach to patients who have early stage CLL is monitoring, with no treatment. The life expectancy of these patients is roughly the same as healthy people of the same age.[v]

In intermediate stage CLL, cancerous cells accumulate in the blood and invade more lymph nodes or other lymphatic organs. These patients are typically treated only if they have symptoms. Patients with advanced disease, which may include severe anemia, poor blood clotting, and liver and spleen malfunction, are treated immediately. The median survival of these patients is roughly 3 - 4 years.[vi]

Recommended treatment options for CLL are Fludara™, an alkylating agent, or a nonanthracycline-based combination regimen.[vii] Recently, the addition of a monoclonal antibody drug has been shown to enhance the effectiveness of many of these regimens. Low dose radiation may be used for local symptoms such as lymph node or spleen enlargement.

Development of Fludara®

Role of NIH

The inventions were made by grantees of the National Cancer Institute (NCI), Drs. John A. Montgomery and Anita T. Shortnacy at the Southern Research Institute. They discovered the anti-leukemia activity of a fluorinated nucleotide analog of the antiviral agent vidarabine. The inventions include insertion of the fluorine atom, which made the compound less susceptible to destruction in the cell, and the development of water-soluble versions that are more chemotherapeutically active. They also discovered a process for higher yield production of the compound. Due to the law at that time, these inventions were assigned to NIH.

The NCI performed the early pre-clinical testing of this compound, submitted an IND, and sponsored early clinical testing and the two phase 2 clinical trials on which FDA approval was based. Once clinical activity was established and FDA approval was pending, the NCI obtained permission from the FDA to distribute fludarabine to patients with CLL who had exhausted all other treatment options ("compassionate use").

The office responsible for technology transfer at the time originally licensed these NIH inventions coexclusively to two companies, but only Berlex Laboratories was able to develop a drug. To promote

R & D Timeline

Patent Applications by Montgomery, et al. 4/78 - 11/82

NCI Initiates Preclinical Testing -- 5/79

Patents #4,188,378, #4,210,745, # 4,357,324 Issued -- 2/80 - 2/82

NCI Initiates Clinical Testing -- 1983

Berlex License Signed 1/84

Pivotal Phase II Clinical Trials -- 1/84 - 5/88

Berlex Does Additional Toxicity Studies 11/88 - 8/89

Berlex Analysis of Data From Pivotal Trials 12/88 - 9/89

FDA Approved Fludara™ 4/91

First Commercial Sale 12/91

Berlex License Expired 2/03

broader commercial use of the technology in the long term, the license agreement gave Berlex exclusive use of the invention for only five years after the first commercial sale of a product; Berlex's exclusivity expired well before expiration of these patents. Although these inventions were available to other companies for over six years, no one expressed interest in a license. Berlex's license expired when the last NIH patent expired, in February 2003.

Role of Berlex

The Berlex team worked closely with the NCI as soon as the license was signed. Fludara™ is difficult to manufacture, and the NCI needed increasing amounts. Berlex was responsible for supplying the drug to the NCI for use in a variety of clinical studies, and also for ensuring that NCI had sufficient Fludara™ to provide to compassionate use patients. Berlex was also solely responsible for collecting and analyzing the data from the pivotal phase 2 trials on which FDA approval was based. In addition, Berlex conducted the additional animal and toxicity studies necessary to bring the drug to market.

Public Health Benefits

Fludara™ provides more healthy years for more people -- studies consistently demonstrate that Fludara™ produces more and longer remissions than other therapies for CLL. Fludara™ also ushered in a new era of combination therapy for CLL that is proving highly effective. When Fludara™ is combined with cyclophosphamide or rituximab the response rate reaches 90%.[viii] And because it acts on multiple enzyme pathways, clinicians and researchers are exploring the potential of Fludara™ to improve the efficacy of other chemotherapeutic agents.

Fludara™ is at the forefront of research on new approaches to a wide array of cancers. For example, Fludara™ has enabled the development of a less dangerous form of bone marrow transplant called non-myeloablative bone marrow transplantation, or "mini-transplant."[ix] In this procedure, only the patient's cancer and immune cells are destroyed before the healthy donor stem cells are injected; the bone marrow is spared. The availability of Fludara™ has allowed development and exploration of this new procedure because it is highly effective in eliminating cancer cells and immune cells but does not destroy bone marrow. If this research proves fruitful, it could benefit people with many types of cancer, not just CLL.

In the story of cancer research, Fludara™ is a major success. It has already helped thousands of people with CLL, and the chapter on Fludara ™ is still being written.

References

[i] Triton Biosciences, Inc, licensed these inventions and worked with NCI to develop Fludara. In 1991, Berlex Laboratories acquired Triton, and became the licensee and sponsor of the drug. References here to Berlex include work by Triton.

[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] National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology - v.1.2003, "Non-Hodgkin's Lymphoma, Version 1.2003."

[vi] Keating, MJ, "Chronic Lymphocytic Leukemia," Seminars in Oncology, Vol 26, No 5, Suppl 14 (October) 1999:107 - 114.

[vii] National Comprehensive Cancer Network, Clinical Practice Guidelines in Oncology - v.1.2003, "Non-Hodgkin's Lymphoma, Version 1.2003."

[viii] Byrd, J.C. et al. "Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712." Blood, 1 January 2003, Volume 101, Number1. Schiavone, EM, et al. "Fludarabine plus cyclophosphamide for the treatment of advanced chronic lymphocytic leukemia." Eur J Haematol 2003: 71:23 - 28.

[ix] Keating, MJ "Management Strategies of Chronic Lymphocytic Leukemia." Medscape Clinical Update, 30 May 2003.

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