

Missouri Cancer Care Perspectives

Volume 4, Number 2 • 2004

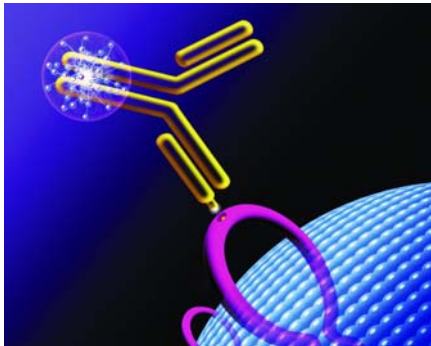
Available at MCC-Wentzville

Zevalin Helps Patients Who Have Failed Standard Therapies

The first radioimmunotherapy medication approved by the FDA and used for the treatment of non-Hodgkin's lymphoma (NHL) is available at Missouri Cancer Care through its Wentzville facility. MCC is the only site in St. Charles to provide the regimen called Zevalin. It is administered locally by John Bedwinek, M.D., a radiation oncologist.

Zevalin is prescribed for select NHL patients who have failed to respond to, or who have become resistant to conventional treatments including chemotherapy and Rituxan.

Virtually all patients with NHL demonstrate a pattern in which they initially respond to treatment, but then



experience a recurrence of the disease with progressively shorter remissions.

Although not a cure, Zevalin provides longer treatment-free periods. It works by delivering radiation directly to the tumor by way of the bloodstream. Zevalin accomplishes this as it is a radioactive isotope linked to a genetically engineered monoclonal antibody. When injected, the monoclonal antibodies circulate through the body until they locate a specific protein on the surface of NHL cancer cells. They latch on to the protein to deliver the radiation.

Zevalin kills not only the cell that it attaches to, but other cells within a five millimeter radius. ■

Chronic Myelogenous Leukemia

When Gleevec No Longer Works: Overcoming Drug Resistance

Approved by the FDA in 2001, Gleevec (imatinib mesylate) has supplanted interferon to become the new standard of care for patients with chronic myelogenous leukemia (CML). It provides better and more durable response rates, with significantly fewer side effects. But it is not considered a cure.

Produced by Novartis Pharmaceutical, Gleevec helps control CML by targeting the product of the BCR-ABL gene mutation. This gene mutation triggers production of an abnormal protein that causes white blood cells to proliferate uncontrollably.

Gleevec — a tyrosine kinase inhibitor — latches on to the abnormal protein, interrupting the cancerous cells' signal to self-replicate.

Although it has been used in all stages of the disease, Gleevec is most effective in patients with early chronic-phase CML. "Virtually all respond at this stage," said Robert Kraetsch, M.D., hematologist and medical oncologist at Missouri Cancer Care. But some patients subsequently develop resistance to the drug and suffer a relapse.

"We are now refining how we use Gleevec, finding out why it doesn't work in some people and learning how to overcome that resistance," continued Dr. Kraetsch.

Secondary mutations in the BCR-ABL gene cause some patients' resistance to the drug. However, the discovery of new cellular pathways is helping target genetic mutations responsible for resistance to Gleevec.

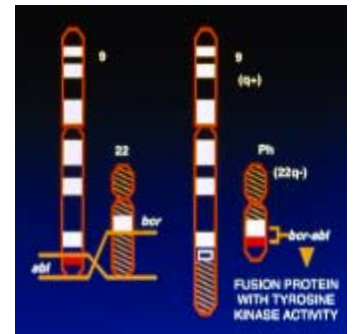
Consequently, drugs are now being developed to attack those pathways.

Two promising but experimental compounds under study target the BCR-

ABL gene itself. Still known by their pharmaceutical number, they are BMS-354825 and AMN107.

BMS-354825 overcame 14 of 15 known mutations — in lab tests

Manufactured by Bristol-Meyers Squibb, BMS-354825 is a dual BCR-ABL and an Src kinase inhibitor. In laboratory tests conducted with mice, the new compound — an oral agent — overcame 14 of the then known 15 mutations that cause Gleevec resistance. More mutations have since been identified.



AMN107 was more potent than Gleevec in preclinical trials

Manufactured by Novartis, AMN107 is also a BCR-ABL inhibitor for patients in accelerated phase or blast crisis CML. Preclinical studies have shown the agent to be 10 to 30 times more potent than Gleevec. Purportedly it is active in some Gleevec-resistant cells.

R115777 (Zarnestra) targets the RAS pathway

Another novel drug under development for CML targets the RAS pathway. Developed by Johnson and Johnson Pharmaceutical — R115777 (Zarnestra) — is a farnesyl transferase inhibitor. It blocks the function of the enzyme, which is needed to activate the RAS gene. This gene acts like a growth factor "on-off" switch. Genetic mutations can keep the gene in the "on" position and stimulate cancer cell growth. ■

Investigational agents target signaling pathways of drug-resistant cancer mutations

May pave way for next generation of targeted therapies

Alternatives To Heparin

New classes of anticoagulants that target specific sites on proteins are evolving. Alternatives to heparin, these new compounds are easier to administer and require less or no laboratory monitoring.

One such agent currently available for use in the United States is Arixtra (fondaparinux). Made by Sanofi-Synthelabo, it is the only FDA-approved antithrombotic for hip fracture surgery.

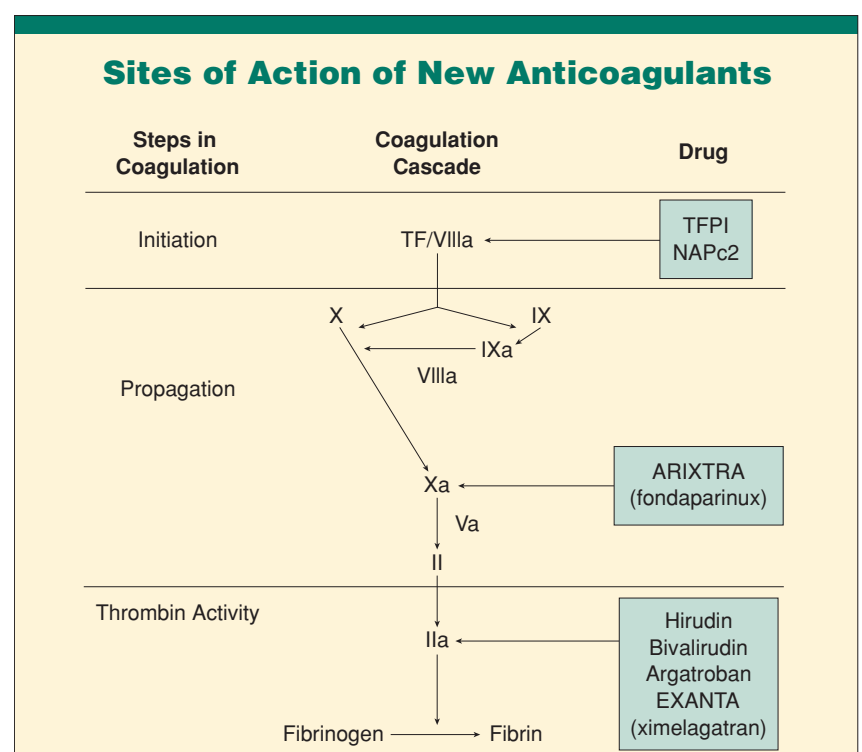
Arixtra selectively inhibits factor Xa, a key component in blood clotting. By binding only to this protein, Arixtra produces fewer side effects than heparin. It is administered once a day by subcutaneous injection and does not require laboratory monitoring as frequently as other agents.

According to results of an analysis presented at the 45th annual meeting of the American Society of Hematology (ASH), Arixtra also appears to be more cost-effective and achieve greater clinical benefit than does enoxaparin for patients following hip surgery.

Another new anticoagulant garnering attention but not approved in the United States is Exanta (ximelagatran) by AstraZeneca. It is the first in a new class of drugs called direct thrombin inhibitors (DTIs).

This oral agent is administered twice a day as a fixed dose. Exanta is rapid acting — it is biologically active within two hours — and requires no follow-up blood tests to monitor its effectiveness. It does not have any known food or drug interactions, but there have been questions about the risk of liver damage from long-term use.

Exanta is available in Germany, Sweden, Portugal and Finland for the prevention of venous thromboembolic events in patients undergoing elective hip or knee replacement surgery. However, its approved use in European Union calls for the first dose to be injected post-operatively. Then the drug is administered orally in pill form. ■



ASH Education Program Book (2000); pg. 266-284. (Altered with permission.)

Novel Therapies And Biologic Agents for Bone Marrow Cancers

A variety of new agents and approaches are available to treat multiple myeloma and myelodysplastic syndromes. One of them includes Velcade (bortezomib) — the first in a new line of anticancer agents known as proteasome inhibitors.

Proteasome inhibitors block “digestive” function of cells

“Proteasomes are found in all cells. They play a ‘digestive’ role by degrading proteins that control cell growth and survival. So they are totally different from other drug targets,” said Robert Kraetsch, M.D., MCC hematologist.

Velcade works in the nucleus as a proteasome inhibitor. By blocking proteasome function, Velcade can lead to cancer cell death. Velcade is not a cure for a myeloma, however. Administered by intravenous injection, Velcade is indicated as a third-line treatment for patients with myeloma.

Velcade received fast-track approval from the Food and Drug Administration in 2003. Its effectiveness is based upon response rates — 28 percent — from clinical studies. As of yet, there are no controlled trials indicating survival benefit. Velcade was co-developed by Millennium Pharmaceuticals and Johnson & Johnson.

Benefit patients with Myeloma & Myelodysplastic Syndrome (MDS)

Thalidomide makes a come-back as treatment for myeloma

Initially used in the 1950s to treat morning sickness but linked with birth deformities, Thalomid (thalidomide) has found a new application for treating myeloma.

Thalidomide is part of a class of drugs known as immunomodulatory drugs (IMiDs), i.e., they can modify or regulate the immune system. IMiDs also have anti-angiogenetic properties. They can block the blood supply to cancerous tumors, perhaps by inhibiting the growth factor VEGF.

In clinical testing, thalidomide produced complete or partial responses as well as disease stabilization in patients with newly diagnosed, refractory and recurrent myeloma.

Produced by Celgene Corporation, thalidomide can be taken as a single agent or in combination with other drugs. According to information released in May from the drug’s maker, and based on data from 26 phase II studies, thalidomide works better for multiple myeloma when combined with other oncologic agents. Thalidomide is used to treat early and advanced multiple myeloma.

Thalidomide derivatives used to treat myeloma & MDS

The Celgene Corporation has two other promising immunomodulatory derivatives (IMiDs) in its drug development pipeline. Purportedly they are more potent than thalidomide and produce fewer side effects. Like other IMiDs, both are oral agents. They are Revlimid (formerly called Revimid) and Actimid (CC-4047).

“Revlimid is believed to work by increasing the ability of the immune system to attack tumor cells,” said Dr. Kraetsch. It has been used for multiple myeloma and MDS.

Still under clinical testing, Revlimid has shown success in increasing the production of red blood cells. This, in turn, may mean fewer blood transfusions for those with MDS.

If approved by the FDA, Revlimid is expected to replace its parent drug, thalidomide.

Like Revlimid, Actimid is a thalidomide analog. It has shown promise in a clinical study for those with relapsed and refractory multiple myeloma. Actimid is believed to affect multiple pathways in myeloma cells. “It’s not as far along in testing as Revlimid,”

continued Dr. Kraetsch. Actimid is not FDA approved.

Vidaza is first drug approved for MDS

Vidaza (azacitidine) is the first drug for treating patients with MDS approved by FDA. “It’s for people with high-risk MDS. It’s for people with frequent transfusion dependency and with increased ‘blasts’ in their marrow,” continued Dr. Kraetsch. Produced by the Pharmion Corporation, Vidaza is approved for treating all five MDS subtypes, and has been available only since July 1.

“This is a drug that I treated a patient with in a study 15 years ago when I was at Barnes,” continued Dr. Kraetsch. “But MDS is a fairly rare disease and the drug has taken such a long time to develop.”

Vidaza is the first of a class of new drugs known as “demethylation” agents. It interferes with the growth of rapidly dividing cells, like cancer, and causes them to die. “Vidaza works fairly well in certain patients,” said Dr. Kraetsch. “Many patients with MDS can be rendered transfusion-independent (with it).” ■

Chronic Lymphocytic Leukemia

Presence of Protein is Strong Predictor of Disease Progression

Chronic lymphocytic leukemia (CLL) is a common hematological malignancy typically affecting adults age 50 plus. CLL occurs when abnormal white blood cells (B lymphocytes) accumulate and depress red blood cells and platelet production.

In many patients, CLL takes several years, possibly decades, to progress. Other patients are not so fortunate, and although rare, can succumb to the disease within a few months. At times, CLL is a disease whose course may be difficult to predict.

Mutations in rearranged IgVH genes have been associated with slow-to-progress CLL. Conversely, the absence of mutations has been the strongest predictor of aggressive disease — but not always.

Researchers believe they have identified a better indicator: an abnormal protein called ZAP-70 expressed by unmutated B-cell receptors and found in the blood and marrow. ZAP-70 increases the signaling capacity of the B-cell receptors thereby stimulating growth of malignant cells.

Prognosis better for those with < 20 percent expression of ZAP-70

An article published recently in *The New England Journal of Medicine* (351: 893-901, 2004) confirms earlier studies about the predictive power of ZAP-70 in CLL patients.

Researchers with the study also determined that patients with a < 20 percent expression of ZAP-70 in their CLL cells had a median 10-year survival whereas patients with a >20 percent expression had a median survival of less than five years. And, because ZAP-70 levels appeared to be constant over time, the study’s authors further suggest that ZAP-70 be used at the time of diagnosis to identify patients at risk for rapid disease progression.

“The gist of the article is that ZAP-70 is a better predictor of aggressive disease than the immunoglobulin heavy-chain gene mutation, and that the two (methods) together were better than one alone,” said Robert Kraetsch, M.D., a hematologist at MCC.

“(ZAP-70) is a surrogate or substitute marker for an immunoglobulin gene rearrangement that correlates with a prognosis,” continued Dr. Kraetsch. “So if we have a young patient with CLL, we can perform this test on their bone

marrow or blood, and give them some idea of their prognosis. If the ZAP-70 is apparent in fairly small amounts, they have a better prognosis. If it is apparent in large amount, they have a fairly bad prognosis and should be followed more closely, and perhaps treated more aggressively.”

Treatment has evolved to produce higher response & longer survival rates

Historically, the approach to treating CLL was based on alkylating agents such as Leukeran (chlorambucil) and Cytosan (cyclophosphamide) used sequentially.

“They give high response rates in CLL,” continued Dr. Kraetsch. “Many people go into remission, sometimes for lengthy periods of time, but everyone eventually relapses.”

Fortunately a new category of drugs became available.

“The first of a new class of drugs called purine analogs was introduced about 15 years ago,” said Dr. Kraetsch. Probably the best known in this category is Fludara (fludarabine). “By itself, fludarabine gave even higher response rates but it also has high risk of infectious complications.”

Then came the advent of monoclonal antibodies. The first of these targeted therapies was Rituxan (rituximab). Initially, the response rate of CLL in a pivotal pilot study was low. Newer approaches have increased dose intensity, which have improved response rates. Rituxan is currently being used in conjunction with Fludara and Cytosan in CLL. “This three-drug (FCR) regimen developed at M.D. Anderson Cancer Center gives a very high complete remission rate, an overall response rate of 95%,” said Dr. Kraetsch.

“But we know that patients will fail eventually requiring treatment down the road, and that their (cancer) cells have probably become resistant to prior drugs. We also know that microscopic disease is never eradicated completely. There is always a surviving cancer cell.

“So the thought today is perhaps we can eliminate that small group of leukemic cells with another agent when people are in complete remission,” continued Dr. Kraetsch. “Then perhaps stem cell transplants might eventually allow for a cure in some people.”

One new agent that is hoped to buy patients more time, and clean up residual disease is a promising new monoclonal antibody called Campath (alemtuzumab). However, it does have significant immunosuppressive side effects.

“Suffice it to say we have new drugs and combinations of older drugs that can be put together for higher response rates and longer survival for patients with CLL. I’m not saying this disease is now curable, but progress has been made.” ■

Current treatment combines older agents with new therapies for better results

From Our Point of View

Many patients do not have cancer, yet benefit from expertise provided by our hematologists.

Approximately 40 percent of referrals coming to Missouri Cancer Care are for non-malignant hematological problems. They include anemias of various kinds, bleeding disorders, deficiency states and a wide variety of primary bone marrow disorders.

In this issue of *Perspectives*, we address advancements in treating hematological conditions, benign and malignant. Topics include new oral alternatives to heparin, overcoming Gleevec resistance in chronic myelogenous leukemia, and information about a protein believed to be a strong prognostic indicator for patients with chronic lymphocytic leukemia.

Ideas and professional guidance for this issue were provided by Dr. Robert Kraetsch. An adjunct associate professor of medicine at Washington University, Dr. Kraetsch is triple board certified in internal medicine, medical oncology and hematology. However, his practice emphasis at Missouri Cancer Care is hematology. He is also the only board-certified hematologist in St. Charles County. ■

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