Signal Transduction Inhibitors:

A BRAND NEW WORLD

Driven by continued clinical and laboratory research, the treatment of chronic lymphocytic leukemia (CLL) has come a long way. It has evolved from single agent chemotherapy to multiagent chemotherapy, and more recently, to the combination of chemotherapy with monoclonal antibodies – so called "chemoimmunotherapy". Patients have benefitted greatly from these advances, with improved rates of complete remission and a higher fraction of durable long term remissions.

Although these advances have been made and some battles have been won, the war against CLL continues, and challenges still remain. Chemoimmunotherapy is often limited by infusion reactions, chemotherapy toxicities, and low blood counts that are often not tolerated in older patients. Relapsed or resistant disease continues to be a clinical challenge and an important area of research.

As more is learned about the biology of CLL, it is becoming apparent that the next advances in the treatment of CLL will come in the realm of blocking signal transduction- the mechanism in which cells receive and send signals in order to function.

Several groups of CLL investigators have uncovered the importance of the B-cell receptor (BCR), which is an important protein that sits on the outside of a malignant CLL cell. Through this receptor, the CLL cell is able to receive signals from its external environment.

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These signals are important in supporting the survival of the cancer cell, stimulating it to grow and also promoting retention of CLL cells in the tissues where they are sheltered from the effects of standard chemotherapy. Scientists have found that the signals through this receptor are communicated through a network of different proteins within the cell.

Among the proteins that make up this communication network are: Syk, Lyn, Btk, and PI3K. If one or several of these proteins could be disrupted by a targeted drug, signals through the receptor could be effectively blocked. As a result, the malignant CLL cell would not receive the appropriate signals to grow, survive and hide from chemotherapy. This could potentially lead to the release of the CLL cells from the tissues and subsequent death. This also could make them more sensitive to standard chemotherapy.

Investigation into these signaling proteins has led to the development of several drugs that target them. Drugs that target Syk, Btk, Lyn, and PI3K are currently in clinical trials in patients with CLL to study their efficacy (see table below). A major feature of these drugs is that they are given by mouth and have very few recorded side effects.

If these drugs show promising activity, future trials using them in combination with other CLL drugs such as chemotherapy or monoclonal antibodies may be planned. Such combinations can help to address the challenges of relapsed and resistant disease and perhaps further improve current remission rates. ::

SYK INHIBITOR/FOSTAMATINIB

Oral inhibitor of the Spleen tyrosine kinase (Syk). Phase I/II clinical trial completed in B-cell lymphoma/CLL. Results presented at 2008 American Society of Hematology Annual Meeting demonstrated fostamatinib to be very active against CLL. Most recent research on this agent has been focused on rheumatoid arthritis (RA). A paper published in *The New England Journal of Medicine* demonstrated a very significant improvement in the outcome of RA. Thus it is very likely that this drug will come back to the CLL research environment.

BTK INHIBITOR/PCI-32765

Phase I clinical trial currently ongoing for untreated and previously treated CLL patients. The oral compound has shown significant inhibition of a key enzyme, Btk (Bruton's tyrosine kinase), which plays a role in B-cell activation. Initial reports suggest that a majority of patients are responding to the therapy. Lymph nodes shrink dramatically within a period of weeks. B-cells are liberated and move from the lymph glands into the body's circulation where they become more susceptible to either attack by other agents or to natural death.

LYN INHIBITORS/DASATINIB & BAFETINIB

Lyn kinase is another key enzyme in CLL cells that is responsible for cell survival. Laboratory studies show that inhibition of Lyn kinase in CLL cells results in the death of CLL cells. Drugs that have the ability to inhibit Lyn kinase should have some effect on CLL cells. Both dasatinib and bafetinib are currently being studied in CLL patients. Results from these studies will provide useful information.

PI3K INHIBITOR/CAL-101

Another important enzyme is PI3 kinase delta. This enzyme is inhibited by an agent called CAL-101 which has been demonstrated to be very active in CLL. Ongoing studies include a trial examining the combination of CAL-101 and rituximab in elderly patients with previously untreated CLL or SLL (small lymphocytic leukemia). There is also an ongoing study in conjunction with bendamustine.