Ibrutinib has 'unprecedented' impact on mantle cell lymphoma

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An international study of ibrutinib in people with relapsed or refractory mantle cell lymphoma (MCL) continues to show unprecedented and durable results with few side effects.

Researchers from The University of Texas MD Anderson Cancer Center presented interim findings of the multi-center Phase 2 study today at the 54th American Society of Hematology Annual Meeting and Exposition.

"I believe we are witnessing a breakthrough in mantle cell lymphoma. This is great news for patients," said Michael Wang, M.D., associate professor in MD Anderson's Departments of Lymphoma and Myeloma and Stem Cell Transplantation and Cellular Therapy. Wang is lead author of the study.

Wang, director of the mantle cell lymphoma (MCL) program at MD Anderson, has spent the past 12 years researching the disease, including clinical trials of proteasome inhibitors, immune-modulating agents and an mTOR inhibitor.

"In a heavily treated relapsed or refractory population, oral ibrutinib induced a response rate as high as 70 percent - better than any other single agent ever tested in MCL," he said. "The response is durable with a long progression-free survival. "

Dangerous disease presents treatment challenges

MCL is a rare and aggressive B-cell subtype of non-Hodgkin lymphoma that, according to the Leukemia and Lymphoma Society, accounts for 6 percent of non-Hodgkin cases. Despite high response rates to initial combination-drug chemotherapy, which is highly toxic, patients often relapse.

Bruton's tyrosine kinase is a mediator of B cell receptor signaling, which is essential for normal B-cell development. Ibrutinib inhibits Bruton's tyrosine kinase (BTK), causing cell death and decreasing cellular migration and adhesion in malignant B-cells.

"The foundation for this clinical success is based on biology," Wang said. "The B-cell receptor pathway is critical in B-cell lymphoma. BTK is the driver molecule in this pathway, and ibrutinib targets the BTK molecule."

Oral medication

Preliminary results reported at ASH in 2011 included 51 patients and demonstrated ibrutinib can achieve rapid response, including complete response, in relapsed and resistant MCL.

To date, 115 people have enrolled in the study. Of these patients, 110 were evaluated for the drug's efficacy. Patients had a median age of 68 years, time since diagnosis of 42 months, three prior treatments and 77 percent had stage 4 disease.

Ibrutinib was given orally at 560 mg daily in continuous 28-day cycles until disease progression.

Strong results, low toxicity

With a median follow-up period of 9.2 months, overall response rate was 68 percent, and complete remission rate was 22 percent.

Responses increased with longer time on study treatment:

- Median time to partial response was two months
- Median time to complete remission was four months
- Median time on treatment was six months
- 53 percent of subjects remain on treatment

Response was even more dramatic in the 51 original patients with:

- Overall response rate of 75 percent
- Complete remissions in 39 percent
- Median time on study treatment 15 months

"What impressed me the most is the high complete remission rate, which continues to improve with time, and yet it is the safest drug we have for mantle cell lymphoma," Wang said. "Previously such a rate could be achieved only with combination cyto-reductive chemotherapy, which is bone marrow suppressive and toxic."

Most side effects were minor and included diarrhea, fatigue, upper respiratory tract infections, nausea and rash. Grade 3 or higher effects included low white cell blood counts, anemia and diarrhea. One case of pneumonia was thought to be treatment-related. This was consistent with safety data previously reported, Wang said.

A pivotal study in relapsed and refractory MCL patients following bortezomib treatment has begun.

Provided by University of Texas M. D. Anderson Cancer Center