Idelalisib Effectively Treats Indolent Lymphoma

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Indolent non-Hodgkin's lymphoma (iNHL) is a slow growing cancer affecting B-cells. These lymphomas are difficult to treat with radiation and chemotherapy, and patients eventually relapse and become resistant to therapy over time. Prognosis is worse for patients who do not respond to standard therapies, necessitating the development of novel drugs. Lead author Dr. Ajay Gopal of the Clinical Research Division and collaborators report promising results in *The New England Journal of Medicine* from a Phase 2 study with the targeted inhibitor idelalisib in treatment of iNHL patients relapsed or refractory to standard treatment. "Idelalisib and other similar agents shift the paradigm from toxic chemotherapy that can only be given for a limited period to time to safer chronic, oral, therapy that can potentially control the disease for long periods with fewer side effects," according to Dr. Gopal.

Idelalisib is a small molecule inhibitor of phosphoinositide 3-kinase (PI3K) delta, an isoform of the lipid kinase found only in hematopoietic cells. This makes PI3Kdelta an attractive target for blood cancers, as its inhibition would in theory have limited toxicity against healthy cells in other tissues. PI3Kdelta is activated downstream of a number of receptors present on B cells, including the B-cell receptor, cytokine and chemokine receptors, and integrins. Notably, malignant B cells rely on PI3Kdelta activity for cell growth, survival, and motility (see figure).

Dr. Gopal contributed to all stages of the clinical trial including the design of the study, the treatment of patients, and the analysis and presentation of the data. The Phase 2 efficacy and safety study for idelalisib enrolled 125 iNHL patients aged 33 to 87 who did not respond to conventional therapies or had relapsed within six months of treatment. Patients were treated in the Seattle area and at 17 additional institutions in the United States and Europe. The Seattle-based company Gilead Sciences, Inc. funded the clinical study. Patients received 150 milligrams of idelalisib twice daily. Tumors shrunk by at least half in 57 percent of patients that received idelalisib (95 percent confidence interval, 48 to 66), and in 6 percent of patients there was no detectable cancer. Responses were rapid and durable, with the median time to a response at 1.9 months and the median duration of response at 12.5 months. At the time of data cutoff, the median overall survival was 20.3 months (range, 0.7 to 22.0) and the median progression-free survival was 11 months (range, 0.03 to 16.6).

Idelalisib is a more targeted approach to treating cancer with fewer side effects than standard chemotherapies. The standard treatment for iNHL involves a combination of chemotherapy and rituximab, an antibody that targets the cell surface protein CD20 found on B cells. Life-threatening complications of these treatments include infections and bone marrow failure. The most common side effects of idelalisib treatment were diarrhea, fatigue, nausea, cough, and fever. Adverse cases of diarrhea and colitis occurred in 13 and 4 percent of patients respectively and were managed with adjustments in the drug dose.

Impressively, this clinical trial demonstrates that targeting a specific kinase can safely induce responses in the vast majority of treatment-refractory iNHL patients. Dr. Gopal says this approach "opens the door to kinase-targeted therapies that can yield low-toxicity control of these otherwise incurable diseases." Dr. Gopal compares this approach to the treatment of hypertension. "It is hard to cure hypertension, but as long as you control it you will not suffer the sequelae."

In the same issue of *The New England Journal of Medicine*, another clinical study demonstrated significant antitumor activity with idelalisib in combination with rituximab in chronic lymphocytic leukemia (CLL) patients who relapsed after previous treatments or were unable to undergo standard chemotherapy. Dr. John Pagel also of the Clinical Research Division was a contributor to the CLL study (Furman, *et al*. 2014). Thanks, in part, to positive results such as those reported in the two *NEJM* publications, idelalisib may be approved for treatment of iNHL and CLL in the near future.

Gopal AK, Kahl BS, de Vos S, Wagner-Johnston ND, Schuster SJ, Jurczak WJ, Flinn IW, Flowers CR, Martin P, Viardot A,Blum KA, Goy AH, Davies AJ, Zinzani PL, Dreyling M, Johnson D, Miller LL, Holes L, Li D, Dansey RD, Godfrey WR, Salles GA. 2014. PI3Kδ Inhibition by Idelalisib in Patients with Relapsed Indolent Lymphoma. *N Engl J Med*. Epub ahead of print, doi: 10.1056/NEJMoa1314583.

See also: Furman, R.R., Sharman, J.P., Coutre, S.E., Cheson, B.D., Pagel, J.M., Hillmen, P., Barrientos, J.C., Zelenetz, A.D., Kipps, T.J., Flinn, I., Ghia, P., Eradat, H., Ervin, T., Lamanna, N., Coiffier, B., Pettitt, A.R., Ma, S., Stilgenbauer, S., Cramer, P., Aiello, M., Johnson, D.M., Miller, L.L., Li, D., Jahn, T.M., Dansey, R.D., Hallek, M., O'Brien, S.M. 2014. Idelalisib and Rituximab in Relapsed Chronic Lymphocytic Leukemia. *N Engl J Med.* Epub ahead of publication, doi: 10.1056/NEJMoa1315226.

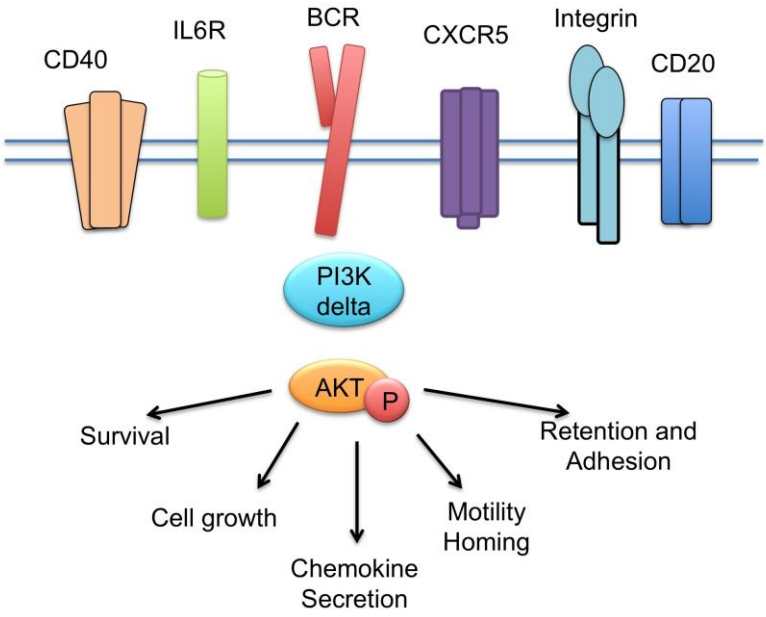

Image created by Valerie Morris

The lipid kinase PI3Kdelta is activated downstream of a number of cell surface receptors present on B cells. In lymphomas, PI3Kdelta activity is increased to promote cancer cell growth, survival and motility. Idelalisib inhibits PI3Kdelta activity and selectively kills lymphoma cells.