Study makes exciting progress in elucidating the mechanisms of bortezomib in lymphoma

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A new study by researchers from the John Theurer Cancer Center at Hackensack University Medical Center sheds light on how bortezomib (VELCADE), the first in a new class of cancer drugs known as proteasome inhibitors, works in mantle cell lymphoma. The study also provides preliminary evidence for which patients might benefit most from bortezomib. Additionally, researchers demonstrate that biomarkers - the genes and proteins that indicate biological processes - might help guide the selection of patients for specific clinical trials and speed-up the development of targeted cancer drugs. The study, which is now published online, will also appear in the July issue of *Leukemia & Lymphoma*.

Bortezomib is a proteasome inhibitor, a new class of cancer drugs that target the proteasome. The proteasome is a critical structure within cells that degrades or recycles more than 90% of intracellular proteins - it breaks down proteins that are meant to be discarded. Studies have shown that if the proteasome is stopped from functioning ("inhibited"), cancer cells, especially myeloma and lymphoma cells, are overwhelmed and die. It is well known that bortezomib binds to one of the enzyme site, called chymotrypsin-like, where proteins are broken down within the proteasome. Given the number of proteins degraded within the proteasome, the consequences of bortezomib on cell function and metabolism are very complex.

"Numerous cellular pathways are regulated by the proteasome, and it has been difficult to determine which are critical to the anti-tumor activity

of bortezomib," said lead author Andre Goy, M.D., M.S., Chief, Lymphoma, the John Theurer Cancer Center. "The data from this study begins to illuminate the drug's mechanisms of action."

Dr. Goy and colleagues performed immunohistochemical analyses of proteins in archived tumor samples from approximately half (73) of the patients who participated in the PINNACLE trial of bortezomib for mantle cell lymphoma, examining the tumors for both the presence and levels of certain proteins that have been associated with tumor growth or cancer cell death in previous genomic studies. Using a statistical software package, they then compared the biomarker levels to the effect of the drug on patients in the trial, grouping patients according to factors such as overall survival and time to progression of their disease. They also analyzed the patients' classification according to two commonly used prognostic scales, in order to see how the scales predicted survival.

Results of the PINNACLE trial, of which Dr. Goy was co-principal investigator, led to the Food & Drug Administration's approval of bortezomib for a defined group of mantle cell lymphoma patients.

"Both the current study by Dr. Goy and the PINNACLE study, which he co-led, highlight ways in which the John Theurer Cancer Center is working at the forefront of personalized medicine to develop better therapies, as well as to understand the basic mechanisms of cancer and its treatment," said Andrew L. Pecora, M.D., F.A.C.P., C.P.E., Chairman and Executive Administrative Director, the John Theurer Cancer Center. "We are proud to be taking a leading role in this important research."

Personalized medicine is a young but rapidly advancing field of health care that was given additional impetus by the sequencing of the human genome. This type of medicine is informed by each person's unique information, including their genetic and genomic profiles. Because these

factors are different for each person, the nature of diseases—including how they might respond to drug therapies — is also different.

Developing personalized treatments - often with the aid of biomarkers - is a major focus of clinical trials in cancer. Drugs known as "targeted" therapies - medications that target specific molecules in tumors and spare healthy cells - are the main focus of personalized medicine-related clinical trials in cancer. Among the oncology drugs already on the market that fall within this category are Gleevec®(Imatinib) and Herceptin®(trastuzumab).

In the current study's examination of biomarkers of interest, the researchers found that elevated Ki-67, a protein associated with cell proliferation, was a marker of poor prognosis. Elevated NF-KB measured by p65, a subunit of a protein complex that plays a key role in inflammation, immune response and cell survival, demonstrated a trend toward longer time to disease progression, longer overall survival and better response. Low levels of PSMA5, another protein that makes part of the proteasome itself and is used to measure the proteasome activity in the cell, were correlated with better response and longer time to progression. Elevated levels of p27, a tumor suppressor protein, which accumulates after proteasome inhibition, were significantly associated with longer overall survival as well.

"There are a multitude of pathways these types of drugs may affect," said Dr. Goy. "The biomarkers help us identify the most promising. Moving forward, this will give us new tools to see how cells are wired and identify those patients who might benefit most from a particular drug."

Dr. Goy pointed out that this study is the first to look at biomarkers in lymphoma using bortezomib. He believes that the study demonstrates that clinical trials can be better designed in the future so that phase II

research can answer some of the questions currently addressed in phase III clinical trials. This might be done by entering patients on a given trial based on certain biomarkers that could help predict patient's response, and potentially lead to more rationally-based cancer therapies.

"By preplanning and archiving tumor samples we can later examine the therapeutic effects on patients in various subsets," he said. "Our findings should prove helpful in designing additional studies of bortezomib, as well as in trials of other potential therapies for non-Hodgkin's lymphomas."

Mantle cell lymphoma is an uncommon type of fast-growing non-Hodgkin's lymphoma that affects the body's B cells, a subtype of white blood cells that play important roles in the immune system. Although the median overall survival of mantle cell lymphoma patients has more than doubled in the last 20 years, survival remains in the range of four to five years. Most patients eventually relapse and often develop resistance to the effects of their medication. Bortezomib, which is also approved for use in multiple myeloma, is approved for use in patients with mantle cell lymphoma who have had at least one prior treatment with another drug.

Provided by John Theurer Cancer Center

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