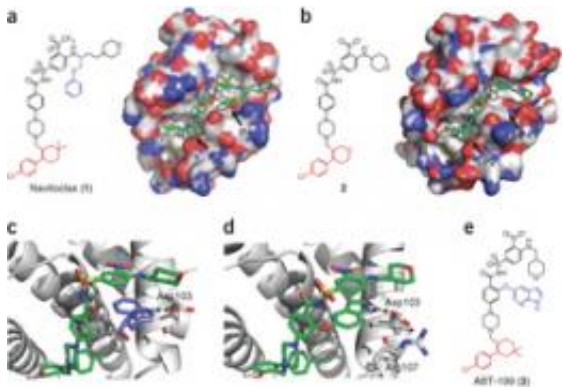
New pill holds promise for fewer side effects in treating leukemia

January 7 2013, by Bob Yirka



Discovery of ABT-199. Credit: *Nature Medicine* (2013) doi:10.1038/nm.3048

(Medical Xpress)—An international team of researchers has developed a new anti-cancer drug that holds promise as a therapy that fights cancer while causing fewer side effects than current medicines. The work done by the group – mainly in the US and Australia – and the results they've achieved are described in an article published by the team in *Nature Medicine*.

The pill, known as ABT-199, works by attacking a key BCL-2 protein that cancer cells use to ward off the beneficial effects of traditional chemotherapy. BCL-2 proteins, known as pro-survival proteins, inhibit the therapeutic effects of chemotherapy which lead to a requirement for large doses and resultant negative side effects such as nausea and hair loss. In this new study, during trials in a medical care facility in

Melbourne, Australia, a single ABT-199 pill was found to "dramatically" reduce the number of leukemia cells in the blood after just an eight hour period while causing few side effects.

BCL-2 (B-cell lymphoma 2) is one of the originally discovered members of the BCL-2 group of cell-death regulator proteins and is evident in the BCL2 gene. It has been seen in a number of cancers and has also been linked to some mental illnesses and autoimmune diseases. When present in cancer, it is believed to work as an inhibitor, providing resistance against cancer treating drugs. The goal of this new work was to develop a drug that would eliminate or reduce the presence of the protein in cancerous cells which would allow chemotherapy to do its job.

One of the main hurdles the team had to overcome was to find a substance that would inhibit the growth of BCL-2 without disturbing the growth of BCL-XL – a protein necessary for platelet development. Because the two are so similar, prior efforts to curb the deleterious protein, generally resulted in harming the helpful one. As trials have continued, it appears the team has overcome this problem as the team reports there have thus far been no adverse impact on BCL-XL levels as tumors have been reduced in patients.

The team came up with the formula for the new pill by studying existing anti-BCL drugs – gradually weeding out the ones that harmed BCL-XL. They report that trials with three patients show that the new pill demonstrates a promising new therapy for treating several types of cancers while simultaneously reducing negative side effects.

More information: ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets, *Nature Medicine* (2013) doi:10.1038/nm.3048

Abstract

Proteins in the B cell CLL/lymphoma 2 (BCL-2) family are key regulators of the apoptotic process. This family comprises proapoptotic and prosurvival proteins, and shifting the balance toward the latter is an established mechanism whereby cancer cells evade apoptosis. The therapeutic potential of directly inhibiting prosurvival proteins was unveiled with the development of navitoclax, a selective inhibitor of both BCL-2 and BCL-2–like 1 (BCL-XL), which has shown clinical efficacy in some BCL-2–dependent hematological cancers. However, concomitant on-target thrombocytopenia caused by BCL-XL inhibition limits the efficacy achievable with this agent. Here we report the re-engineering of navitoclax to create a highly potent, orally bioavailable and BCL-2–selective inhibitor, ABT-199. This compound inhibits the growth of BCL-2–dependent tumors in vivo and spares human platelets. A single dose of ABT-199 in three patients with refractory chronic lymphocytic leukemia resulted in tumor lysis within 24 h. These data indicate that selective pharmacological inhibition of BCL-2 shows promise for the treatment of BCL-2–dependent hematological cancers.