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COMMENTARY

A good molecular target for prostate cancer chemotherapy

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An exciting new basic medical research study shows that inhibition of the activity of the kinesin spindle protein Eg5 effectively blocks cell division and induces cell death in prostate cancer cells.[1] The potent anticancer drug *S*-(methoxytrityl)-L-cysteine (S(MeO)TLC) specifically blocks activity of Eg5 in prostate cancer cells, arrests cell division, induces cell death during mitosis and inhibits prostate cancer cells in a mouse model of prostate cancer.[1]

Prostate cancer is a leading cause of cancer death in men in the United States with over 27 000 deaths due to castration-resistant prostate cancer in 2009.[2] Androgen deprivation therapy is effective with most patients for 1 to 2 years. However, prostate cancer cells become resistant to androgen deprivation and progress to castration-resistant prostate cancer.[3] Patients can then undergo a standard combination chemotherapy based upon mitotic spindle inhibition by taxanes such as docetaxel.[4–6] However, taxanes cause serious side effects such as neurotoxicity,[7] drug-binding site mutations on β-tubulin,[8] and overexpression of P-glycoprotein[9] and β-tubulin.[10] Cancer cells thus develop taxane-related drug resistance. There are no good standard treatment options for patients with castration-resistant prostate cancer when the cancer advances and alternative treatment strategies are urgently needed.

That is why this new study is so important. Eg5, a member of the kinesin-5 motor proteins,[11] is critical for bipolar spindle formation and chromosome separation during mitosis.[12,13] Inhibition of Eg5 by S(MeO)TLC blocks cell division leading to cell death thus providing an option to microtubule-targeted cancer chemotherapy. Eg5 inhibitors overcome multidrug resistance, since Eg5 is not transported out of cells by P-glycoprotein.[14,15] In addition, kinesin spindle proteins such as Eg5 are absent in differentiated neurons.[4] One potent kinesin spindle protein inhibitor ispinesib (SB-71599) is being tested in clinical trials where it appears to be generally well tolerated with mild hematologic and little other toxicity.[4]

In two recent studies involving Eg5 inhibition in prostate cancer, researchers found that docetaxel-resistant and non-resistant prostate cancer cell lines showed sensitivity to antisense oligonucleotide or *S*-trityl-L-cysteine.[16,17] In a previous study by some authors of the present study, the Eg5 inhibitor S(MeO)TLC was 10-fold more potent than the antisense oligonucleotide or *S*-trityl-L-cysteine for inhibition of cell proliferation and it was extremely specific toward Eg5.[18] In another recent study, S(MeO)TLC was shown to have potent anticancer activity in bladder cancer *in vitro* and *in vivo*.[19]

In conclusion, more emphasis is now being placed on therapies that aim at specific molecular targets in tumor cells.[4] In clinical studies of these antimitotics, neurotoxicity has not been observed to a significant degree and neutropenia is the main toxicity. Unfortunately, early studies in their use have been disappointing in terms of efficacy. However, it is hoped that new agents may improve the therapeutic value of this class of drug and that these newer agents may continue to lengthen the survival of cancer patients and improve upon toxicities in the years ahead.

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