



Letter to the Editor

Re: Kim N. Chi, Anders Bjartell, David Dearnaley, et al. Castration-resistant Prostate Cancer: From New Pathophysiology to New Treatment Targets. Eur Urol 2009;56:594–605

Chi et al. [1] correctly identified the strongly antiapoptotic protein BCL-2 as an attractive target in treating men with castration-resistant prostate cancer (CRPC). They also pointed out that inhibiting the expression of that single antiapoptotic protein may not be sufficient to overcome the effect of the other antiapoptotic proteins with expression that is not being inhibited. As the authors mentioned, a new drug, AT-101, inhibits the expression of multiple members of the BCL-2 family, and initial studies indicate that AT-101 is more effective than using a drug that targets only BCL-2. However, there is an alternative approach to targeting BCL-2 that, in theory, has the potential to be curative for some CRPC patients.

If hormone receptors upregulate and downregulate proapoptotic and antiapoptotic proteins in a purposeful manner, then by combining agonism of those hormone receptors that downregulate BCL-2 with antagonism of those that upregulate BCL-2, it should be possible to greatly increase the rate of cell death. This result is possible because those hormones that strongly upregulate BCL-2 should also strongly upregulate the other antiapoptotic proteins. The power of targeting hormone receptors has been demonstrated in the success of using 20 mg/d of toremifene to act as an antagonist of just estrogen receptor- α (ER- α), resulting in a 21.8% reduction in the number of high-grade prostatic intraepithelial neoplasia (HGPIN) patients who develop prostate cancer (PCa) after 12 mo [2]. In the case of late HGPIN, the rate of cell death is equal to the rate of cell growth [3], so that a slight increase in the rate of cell death is effective in preventing PCa from developing; however, for CRPC patients, much more than a slight increase is needed.

To minimize the upregulation of antiapoptotic proteins, antagonists to ER- α , membrane estrogen receptor (mER), progesterone receptor A (PRA), and membrane androgen receptor (mAR) should be administered. To maximize the downregulation of antiapoptotic proteins, agonists to ER- α , progesterone receptor B, membrane progesterone receptor, and intracellular androgen receptor (iAR) should be

administered [4]. Agonism can be achieved readily by administering bioidentical hormones. The use of both 20 mg/d of toremifene [2] as an antagonist for ER- α and 200 mg/d of mifepristone [5] as an antagonist for PRA appears to be safe and effective. No drug is yet available to act as an antagonist for either mER or mAR. If a drug is developed that is a safe and effective antagonist for mAR, it may not be necessary to develop a drug that is an antagonist for mER because iAR upregulates the proliferation arrest protein AS3, whereas mAR downregulates AS3 [4]. Just using all of the existing drugs and hormones plus a drug that acts as an antagonist to mAR should minimize the amount of antiapoptotic proteins while preventing proliferation. In some CRPC patients who do not yet have any mutation that prevents iAR from upregulating AS3, such a combined therapy has the potential to be curative.

Conflicts of interest: The author has nothing to disclose.

References

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