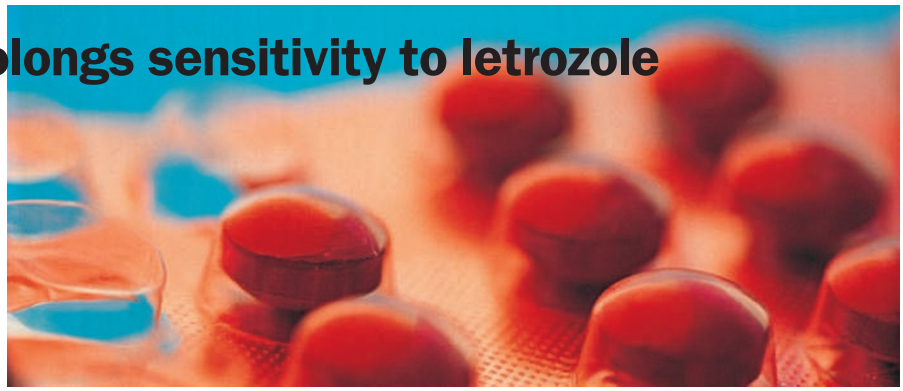
HORMONAL THERAPIES

Treatment break prolongs sensitivity to letrozole



The use of aromatase inhibitors is associated with considerably improved outcomes in postmenopausal women with hormone-responsive breast cancer. Many patients, however, do not respond or experience relapse after treatment. Sabnis and colleagues previously developed a mouse model using human estrogen-receptor-α (ERα) breast cancer cells that were transfected with human placental aromatase gene and grown in ovariectomized female nude mice, in order to simulate postmenopausal breast cancer. Using this model, the researchers had established that aromatase inhibitors were more effective than tamoxifen for treating hormone-responsive breast cancer; however, these responsive tumors eventually developed resistance. Therefore, this group carried out another study to investigate the mechanisms of resistance to aromatase inhibitors and possible ways to reverse resistance so that the use of chemotherapy could be delayed. In this study, the researchers compared the effects of intermittent letrozole treatment with switching treatment between letrozole and trastuzumab on the outcomes on tumor growth. "We concluded that resistance to letrozole was a result of adaptation of tumor cells to a low-estrogen environment through upregulation of Her-2 and downregulation of ERα." comment the authors.

The investigators used a novel hormone-dependent model to identify the mechanism of resistance to letrozole. They found that lack of response to letrozole was accompanied by upregulation of the Her-2/mitogen-activated protein kinase (MAPK) pathway and downregulation of ERα and aromatase activity. In addition, they found that use of trastuzumab to inhibit Her-2 could reverse resistance to letrozole, as could discontinuation of letrozole treatment.

Mice were treated with letrozole until they developed resistance and were then randomized into three groups: one group continued letrozole treatment, the second group were given trastuzumab, and the third discontinued treatment. Every week tumors were collected to assess changes in tumor protein expression and activity, and uteri were also weighed. Sabnis and coauthors noticed that tumors in mice who received 6 weeks of letrozole treatment followed by 6 weeks off treatment acquired resistance quicker than those who received continuous letrozole.

The mice receiving continuous letrozole had significantly lower mean tumor weights than those receiving intermittent letrozole ($P<0.01$). Cyclic treatment consisting of 22 weeks of letrozole treatment, followed by withdrawal for 6 weeks and 6 weeks further treatment did not reduce the tumor volume. Mice who continued to receive letrozole did not experience a change in mean uterine weight, whereas mice who were taken off treatment had increased mean uterine weights. Moreover, the uterine weight of mice treated with trastuzumab was significantly increased, and this finding correlated with an increase in aromatase activity. Upregulation of the Her-2/MAPK pathway was observed in letrozole-resistant tumors accompanied by downregulation of ERα and aromatase.

Fluorescence *in situ* hybridization was used to assess Her-2 upregulation. The *Her-2* gene was not amplified in tumors that were resistant to letrozole. The effect of intermittent treatment was assessed in a MCF-7CA xenograft model. Over the first 9 weeks of the study, the growth rate of tumors treated with letrozole was significantly lower than control tumors ($P<0.0001$). By week 22, the tumors of mice treated with letrozole had doubled in volume, whereby they were assigned to the three treatment groups. There were no differences in tumor growth between the three groups at 26 weeks. The group that did not receive treatment was then split into two: continuation without letrozole or treatment with letrozole; between weeks 26 and 33 the tumor growth rates between the two groups were not significantly different. Compared with the mice treated with continuous letrozole, the mice that were switched back to letrozole had significantly lower growth rate ($P=0.02$).

The mice receiving trastuzumab were split into three groups: trastuzumab, trastuzumab plus letrozole or letrozole. The growth rates across these groups were similar over 32 weeks suggesting that single-agent trastuzumab does not provide any benefit in letrozole-resistant tumors. Additionally, the tumors continued to grow when treatment was switched from letrozole to trasuzumab and back to letrozole or letrozole plus trastuzumab. However, when the mice were given a 4-week break in treatment and then switched back to letrozole, tumor growth was inhibited for 18 weeks.

The results of this study suggest that a period of time off treatment reverses resistance; the intermittent treatment strategy presented in this study could result in prolonged response and disease stabilization in patients.

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Original article Sabnis, G. *et al.* Sensitivity to the aromatase inhibitor letrozole is prolonged after a "break" in treatment. *Mol. Cancer Ther.* **9**, 46–56 (2010)