A mechanism for tamoxifen-induced cancer

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Summary

Breast cancer is very common in women. One of the therapeutic choices to treat breast cancer is selective estrogen receptor modulators (SERMs). These drugs inhibit the estradiol effect on estrogen receptors of breast. Tamoxifen, toremifene and raloxifen are SERMs and they were used for treatment of breast cancer. Tamoxifen and toremifene but not raloxifen have been approved for breast cancer treatment. Tamoxifen can cause benign or in some cases malignant hyperplasia of endometrium, but the exact mechanism is unknown. A recent study demonstrated the MGMT (O6-methylguanine-DNA methyltransferase) degradation activity of tamoxifen. We postulated this was involved in tamoxifen-induced malignancy.

Keywords: Breast cancer; MGMT; Tamoxifen

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Introduction

Breast cancer is the most common cancer in women. In USA 180,000 new cases are diagnosed per year and 40,000 deaths are occurred due to breast cancer. 70% of diagnosed breast cancer cases express α-estrogenic receptor which is affected by hormones. Drugs such as tamoxifen which inhibit the effect of estradiol on estrogenic receptors of breast were used in treatment of this cancer. Tamoxifen also was approved for prevention of breast cancer in women who have risk factors for breast cancer (1, 2).

Hypothesis

Tamoxifen and toremifene are SERMs which were used for treatment of breast cancer. Tamoxifen (but not toremifene and raloxifen) could induce endometrial cancer but the mechanism was not exactly clarified. In the other hand the results of a recent study showed that tamoxifen can increase degradation of MGMT enzyme. MGMT is a DNA repair enzyme removes mutagenic and cytotoxic alkyl group from O⁶ guanine. Decreased activity of MGMT was reported in several cancers including endometrial cancer. According to these facts we hypothesized that the ability of tamoxifen to increase degradation of MGMT was involved in carcinogenesis of tamoxifen.

Evaluation of the hypothesis

Tamoxifen can induce some changes in endometrium (usually benign) including endometrial hyperplasia and endometrial polyp but sometimes can induce cancer. 2 to 3-fold increase in incidence of breast cancer was seen in women who treated by tamoxifen after menopause. Therefore the treatment by tamoxifen should not continue longer than 5 years. Furthermore, endometrial cancer in patients taking tamoxifen had a worse prognosis than control group(3-7). Tamoxifen was also increase the chance of hepatic cancer(8-10).

Mechanism of tamoxifen-induced cancer was investigated. It was demonstrated that tamoxifen reacts with DNA and forms adduct. TAM-DNA adducts have mutagenic properties were found in liver and leukocytes after administration of tamoxifen but not toremifene. Therefore, this was assumed as a mechanism of tamoxifen-induced cancer(11-15). But this hypothesis is conflicting about endometrial tissue as some studies reported the formation of adduct in endometrial tissue while some others did not find association between incidence of endometrial cancer and formation of TAM-adducts(16-22). Also it was demonstrated that toremifene had a equal efficacy with tamoxifen in treatment of breast cancer but it had a better adverse reaction profile (including incidence of endometrial cancer) than tamoxifen(23-25).

Tamoxifen increased the toxicity of alkylating drugs. In a recent study the mechanism was investigated and it was shown that tamoxifen increased the

degradation rate of MGMT. MGMT removes mutagenic methyl group from guanine and consequently make the cell resistant to the mutagenic agents(26). Therefore, degradation of MGMT by tamoxifen makes the cell more susceptible to mutagenic agents (including alkylating drugs)(27). In the other hand, inactivation of MGMT gene was reported in several cancers (28-30), which is clarify the effect of MGMT downregulation in promotion of cancer. MGMT inactivation and subsequent decreased expression of MGMT were also reported in endometrial cancer(31).

![Diagram](image)

**Figure 1. Mechanisms for tamoxifen-induced cancer. We suggested that MGMT degradation is involved in tamoxifen-induced endometrial cancer.**

**Conclusion**

According to conflicting results about formation of TAM-DNA adducts in endometrium and established role of MGMT downregulation in cancer including endometrial cancer, we suggest that degradation of MGMT by tamoxifen is involved in tamoxifen-induced endometrial cancer (Figure 1). To test this hypothesis we suggest the comparison of tamoxifen with toremifene or raloxifen in effect on MGMT expression or toxicity of alkylating drugs which indirectly represents the MGMT activity.
References


