A mechanism for tamoxifen-induced cancer

Jamal Shamsara[1], Javad Behravan[1]

[1]Department of Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

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 (O^6-methylguanine-DNA methyltransferase) degradation activity of tamoxifen. We postulated this was involved in tamoxifen-induced malignancy.

Keywords: Breast cancer; MGMT; Tamoxifen

Corresponding Author:

Dr. Javad Behravan

Department of Biotechnology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran

P O Box 91775-1365

Tel: (+98-5118823255-66)

Fax: (+98-5118823251)

E-mail: behravanj@mums.ac.ir

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 a-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 O^6 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).

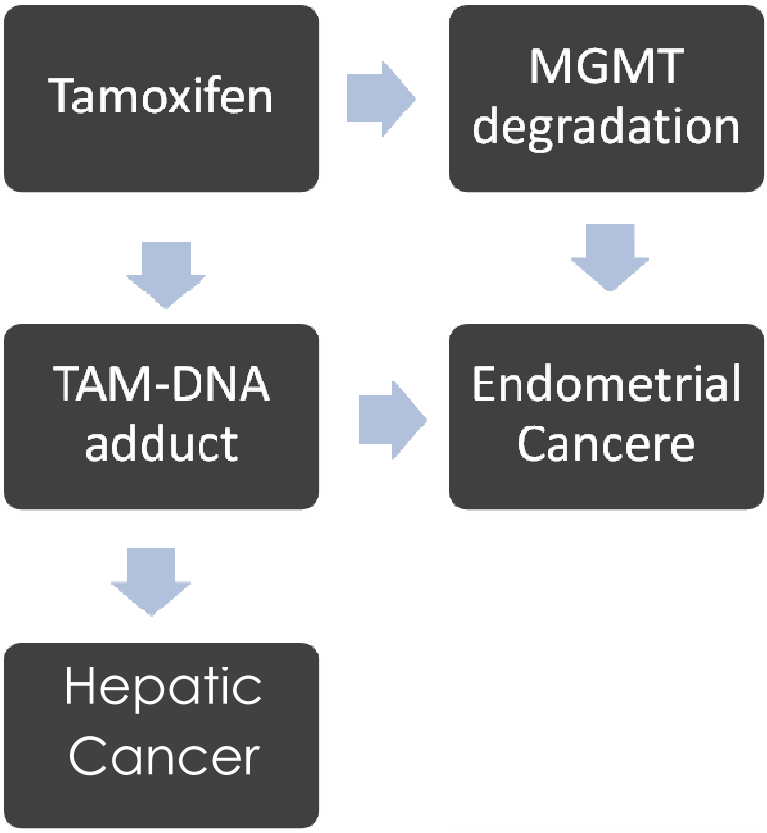

Figure 1. Mechanisms for tamoxifen-induced cancer. We suggested that MGMT degradation is involved in tamoxifen-induced endometrial cancer.

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

1. Jordan VC. Tamoxifen (ICI46,474) as a targeted therapy to treat and prevent breast cancer. Br J Pharmacol 2006; 147 Suppl 1:S269-76.

2. Nichols M. The fight against tamoxifen resistance in breast cancer therapy: a new target in the battle? Mol Interv 2007; 7(1):13-6.

3. Hachisuga T, et al. Clinicopathologic study of 56 patients with endometrial cancer during or after adjuvant tamoxifen use for their breast cancers. Gynecol Oncol 2004; 95(1):139-44.

4. Morales L, et al. Endometrial safety of third generation aromatase inhibitors versus tamoxifen in breast cancer patients. Int J Gynecol Cancer 2006; 16 Suppl 2:515-7.

5. Rieck GC, Freites ON, Williams S. Is tamoxifen associated with high-risk endometrial carcinomas? A retrospective case series of 196 women with endometrial cancer. J Obstet Gynaecol 2005; 25(1):39-41.

6. Saadat M, et al. Outcomes in patients with primary breast cancer and a subsequent diagnosis of endometrial cancer : comparison of cohorts treated with and without tamoxifen. Cancer 2007; 110(1):31-7.

7. Swerdlow A J, Jones ME. Tamoxifen treatment for breast cancer and risk of endometrial cancer: a case-control study. J Natl Cancer Inst 2005; 97(5):375-84.

8. Dragan YP, et al. The effect of tamoxifen and two of its non-isomerizable fixed-ring analogs on multistage rat hepatocarcinogenesis. Carcinogenesis 1996; 17(3):585-94.

9. White I N. The tamoxifen dilemma. Carcinogenesis 1999; 20(7):1153-60.

10. Williams GM, Iatropoulos MJ, Karlsson S. Initiating activity of the anti-estrogen tamoxifen, but not toremifene in rat liver. Carcinogenesis 1997; 18(11):2247-53.

11. Kim SY, et al. Antiestrogens and the formation of DNA damage in rats: a comparison. Chem Res Toxicol 2006; 19(6):852-8.

12. Shibutani S, et al. Mechanism of lower genotoxicity of toremifene compared with tamoxifen. Cancer Res 2001; 61(10):3925-31.

13. Terashima I, Suzuki N, Shibutani S. Mutagenic potential of alpha-(N2-deoxyguanosinyl)tamoxifen lesions, the major DNA adducts detected in endometrial tissues of patients treated with tamoxifen. Cancer Res 1999; 59(9):2091-5.

14. Umemoto A, et al. Absence of DNA adduct in the leukocytes from breast cancer patients treated with toremifene. Chem Res Toxicol 2006; 19(3):421-5.

15. Umemoto A, et al. Determination of tamoxifen--DNA adducts in leukocytes from breast cancer patients treated with tamoxifen. Chem Res Toxicol 2004; 17(12):1577-83.

16. Besaratinia A, Pfeifer GP. Investigating DNA adduct-targeted mutagenicity of tamoxifen: preferential formation of tamoxifen-DNA adducts in the human p53 gene in SV40 immortalized hepatocytes but not endometrial carcinoma cells. Biochemistry 2005; 44(23):8418-27.

17. Carmichael PL, et al. Lack of evidence from HPLC 32P-post-labelling for tamoxifen-DNA adducts in the human endometrium. Carcinogenesis 1999; 20(2):339-42.

18. Carmichael PL, et al. Lack of genotoxicity of tamoxifen in human endometrium. Cancer Res 1996; 56(7):1475-9.

19. Hemminki K, et al. Tamoxifen-induced DNA adducts in endometrial samples from breast cancer patients. Cancer Res 1996; 56(19):4374-7.

20. Martin EA, et al. Tamoxifen DNA damage detected in human endometrium using accelerator mass spectrometry. Cancer Res 2003; 63(23):8461-5.

21. Phillips DH, et al. Organ specificity of DNA adduct formation by tamoxifen and alpha-hydroxytamoxifen in the rat: implications for understanding the mechanism(s) of tamoxifen carcinogenicity and for human risk assessment. Mutagenesis 2005; 20(4):297-303.

22. Shibutani S, et al. Identification of tamoxifen-DNA adducts in the endometrium of women treated with tamoxifen. Carcinogenesis 2000; 21(8):1461-7.

23. Holli K, et al. Safety and efficacy results of a randomized trial comparing adjuvant toremifene and tamoxifen in postmenopausal patients with node-positive breast cancer. Finnish Breast Cancer Group. J Clin Oncol 2000; 18(20):3487-94.

24. Pagani O, et al. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. Ann Oncol 2004; 15(12):1749-59.

25. Pukkala E, et al. Tamoxifen and toremifene treatment of breast cancer and risk of subsequent endometrial cancer: a population-based case-control study. Int J Cancer 2002; 100(3):337-41.

26. Jacinto FV, Esteller M. Mutator pathways unleashed by epigenetic silencing in human cancer. Mutagenesis 2007; 22(4):247-53.

27. Kuo CC, et al. Tamoxifen accelerates proteasomal degradation of O6-methylguanine DNA methyltransferase in human cancer cells. Int J Cancer 2007; 121(10):2293-300.

28. Esteller M, et al. Inactivation of the DNA repair gene O6-methylguanine-DNA methyltransferase by promoter hypermethylation is a common event in primary human neoplasia. Cancer Res 1999; 59(4):793-7.

29. Jones PA, Baylin SB. The fundamental role of epigenetic events in cancer. Nat Rev Genet 2002; 3(6):415-28.

30. Shamsara J, et al. Association between MGMT promoter hypermethylation and p53 mutation in glioblastoma. Cancer Invest 2009; 27(8):825-9.

31. Furlan D, et al. The high frequency of de novo promoter methylation in synchronous primary endometrial and ovarian carcinomas. Clin Cancer Res 2006; 12(11 Pt 1):3329-36.