Inhibition of tamoxifen's therapeutic benefit by tangeretin in mammary cancer

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Abstract

Tangeretin, a molecule present in citrus fruits and in certain 'natural' menopausal medications, is an effective tumour growth and invasion inhibitor *in vitro* of human MCF 7/6 breast cancer cells. However, when added to the drinking water of MCF 7/6 tumour-bearing mice it neutralises the beneficial tumour-suppressing effect of tamoxifen. Tangeretin reduces the number of natural killer cells. This may explain why the beneficial suppressive effect of tangeretin on MCF 7/6 cell proliferation *in vitro* is completely counteracted *in vivo*. © 2000 Elsevier Science Ltd. All rights reserved.

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Overall survival for patients with primary breast cancer is increased by adjuvant therapy with tamoxifen. Resistance to tamoxifen is one of the reasons for treatment failure in mammary cancer patients. Flavonoids from the diet have been implicated in this problem through direct oestrogenic effects on the tumour cells or induction of tamoxifen's liver metabolisation.

Tangeretin, a citrus flavonoid with extensively studied effects on human mammary cancer cells *in vitro*, was tested in combination with tamoxifen in tumour-bearing laboratory mice [1]. Our model consisted of oestrogen-primed female nude mice inoculated subcutaneously with human MCF-7/6 mammary carcinoma cells. Oral treatment of the mice with tamoxifen inhibited the growth of the MCF-7/6 tumours compared with solvent controls ($P < 0.001$ in Student's *t*-test). Tangeretin, added to the drinking water with tamoxifen, completely neutralised the effect of tamoxifen. Furthermore, tamoxifen + tangeretin treatment reduced the median survival time of the tumour-bearing mice compared with the tamoxifen-treated group (14 versus 56 weeks; $P = 0.002$ in Mantel–Cox logrank test). Remarkably, the growth-inhibiting effect of tamoxifen could be reversed upon addition of tangeretin to the drinking water: tumour growth resumed after a median lag period of 14 weeks. Tamoxifen concentrations were not lower in tumours and tissues from tamoxifen + tangeretin-treated mice than in those from tamoxifen-treated ones. The more active metabolite 4-hydroxytamoxifen was undetectable in both groups. Induction of liver metabolisation of tamoxifen by tangeretin was ruled out by high-performance liquid chromatography (HPLC) determinations of tamoxifen and its principal metabolites in tumours, different normal tissues and serum.

Further results indicate that tangeretin is a selective downregulator of lymphokine activated natural killer cells. This reduces the potential to eliminate the tumour cells and explains the extensive tumour growth *in vivo*. Taken together our results plead against the excessive consumption of tangeretin-containing citrus products and nutrition supplement during the tamoxifen treatment of mammary cancer.

References

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