

Prevention of Radiation-enhancement Dermatitis and Breast Cancer Cell Invasion by an Anti-Inflammatory Agent

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For women with early stage breast cancer, the primary tumour is removed by conservative surgery. However, malignant microfoci are often scattered in the breast. To eliminate these cells radiotherapy is designed to irradiate the whole breast. But the dose is not calculated to eliminate all residual cancer cells but rather to optimize long-term results with minimal complications to normal tissues such as fibrosis. These complications are mainly caused by the induction of an inflammation, associated with the upregulation of the cyclooxygenase-2 (COX-2). Furthermore the inhibition of COX-2 decreases matrix metalloproteinases (MMPs) expression, such as MMP-2 and MMP-9, both playing a central role in breast cancer cell invasion. The aim of this study is to further improve radiotherapy of breast cancer by preventing radiation-enhancement dermatitis and breast cancer cell invasion with the administration of NS-398, a COX-2 specific inhibitor.

Female Balb/c mice were irradiated on a healthy thigh followed by the s.c. injection of MC7-L1 mammary cancer cells. NS-398 was injected i.p. before and after irradiation. Controls without irradiation and without cancer cells were also performed. For 3 and 6 weeks the degree of skin inflammation was scored and cancer cell invasion was monitored by contrast-enhanced magnetic resonance imaging. Tumors and surrounding tissues were subsequently removed and processed for histological analysis and zymography.

We have shown that radiation actually enhances the invasiveness of breast cancer cells. MC7-L1 cells grown mainly under the skin in non irradiated thighs but invaded into the muscle fibers in irradiated thighs. These patterns were distinct 4 weeks after irradiation, but more pronounced on the 6th week. The calculated apparent invasion tumor volume was significantly greater in irradiated thighs. The activity of MMP-2 and -9 were enhanced in muscle and skin after irradiation. Our preliminary results with the COX-2 inhibitor NS-398 demonstrated an improvement of skin tolerance and a decrease of the invasion marker MMP-2 in the irradiated area. The NS-398 seemed also to reduce cancer cells proliferation and invasion.

Our promising preliminary data showed that the NS-398, a specific COX-2 inhibitor, might improve the efficacy of radiotherapy for breast cancer by preventing radiation-induced dermatitis and radiation-enhancement of cancer cell invasion.