

Inhibition of adhesion breast cancer cells by anticoagulant drugs and cimetidine*

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Recent studies suggest that anticoagulant drugs and cimetidine therapy in malignancy may improve cancer survival and inhibit the metastatic process.

In this study we investigated and compared the effects of anticoagulant drugs (unfractionated heparin, warfarin, acetylsalicylic acid, low-molecular-weight heparins – nandroparinum, enoxaparinum, dalteparinum and reviparinum), cimetidine and combination of cimetidine with anticoagulants on adhesion of highly invasive breast cancer cells lines – BT 549 and MDA-MB-231 (MDA 231) – *in vitro*.

High antiadhesion effect was observed with cimetidine, warfarin and acetylsalicylic acid. Low-molecular-weight heparins had a small antiadhesion effect in independent use. In combination with cimetidine, a potential effect of cimetidine on the antiadhesion was observed. The antiadhesion effect was dependent on the type of the cancer cell line. Different effects between cell lines BT 549 and MDA 231 were observed. The strongest antiadhesion effect was obtained using the combination of cimetidine with acetylsalicylic acid. In the majority of applications of the drugs and their combinations, a proportional antiadhesion effect was dependent on the concentration and time.

We suppose that anticoagulant drugs might have higher antimetastatic effect in combination with cimetidine. The choice of anticoagulants can decrease the adhesion, decrease tumor angiogenesis and cause the shortening of blood clotting time. Cimetidine can decrease the adhesion of cancer cells and increase the activity of NK cells. Indeed, according to our results, application of cimetidine and anticoagulant drugs intensifies the antiadhesion effect together with other antimetastatic effects.

Key words: Breast cancer, metastasis, adhesion, anticoagulation, cimetidine, heparin.

The metastatic cascade is a very complicated process. It can be divided into four stages [14]: 1st stage – escape from the primary tumor mass and invasion of surrounding tissue, 2nd stage – intravasation, 3rd stage – adhesion to endothelial wall and extravasation, 4th stage – invasion, angiogenesis and growth at a distant site. Very important is the ability of metastatic cells to adhere to the endothelial wall. Long-term circulation in vascular systems decreases the probability of survival of metastatic cells and increases the probability of attack by natural defense system cells.

Advanced breast cancer is frequently associated with hematogenous metastases that are accompanied by serious complications. An increase in morbidity and mortality in breast cancer patients has been frequently observed. Out of 186 examined patients who died of breast cancer, 64% had reported bone metastases at autopsy [23]. This study presented the observation that bone was the second most common site of breast cancer next to lung. The Walther's data demonstrate that the three common sites of distant tumor metastasis are lungs, liver and bone. WEISS [24] autopsied 1 060 breast cases and detected bone metastases in 62%. This frequency was equivalent to that of lung metastases. CIFUENTES and PICKERN [4] found bone metastases in

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