Research Highlight: Neoadjuvant chemotherapy exacerbates breast cancer metastasis.

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Abstract:

In the last decade there has been a rise in the use of neoadjuvant chemotherapy for treatment of cancer patients due to undergo surgery. Although neoadjuvant therapy can reduce tumor size to non-distinguishable levels it does not improve overall patient survival (Rastogi, Anderson et al. 2008, Gianni, Baselga et al. 2009). This paradox is answered by new findings from Karagiannis and collaborators (Karagiannis, Pastoriza et al. 2017), and Chang and colleagues (Chang, Jalgaonkar et al. 2017) who show that though neoadjuvant chemotherapy reduces tumor size, they also increase breast tumor metastasis.

Keywords: Breast cancer, neoadjuvant chemotherapy, metastasis.

Neoadjuvant chemotherapy has been widely used in the last decade for pre-operative tumors. Recent published work by Karagiannis and collaborators (Karagiannis, Pastoriza et al. 2017), and Chang and colleagues (Chang, Jalgaonkar et al. 2017) show that though neoadjuvant chemotherapy reduces tumor size, they also increase breast tumor metastasis.

Karagiannis, et al. using intra-vital imaging show that paclitaxel treated mice have greater vascular leakage and tumor cell dissemination, which occurs from specific site, which they define as the tumor microenvironment of metastasis (TMEM) site. The mechanism which they believe leads to more disseminated tumors is through expression of the invasive isoform of the actin binding protein mammalian enabled (Mena) called MenaINV. Greater MenaINV expression in primary tumor indicates a more aggressive form of breast cancer. The authors after knocking down MENA in mice were able to prevent chemotherapy induced tumor cell dissemination. Next, the authors also show that the effects are not only limited to paclitaxel, but to a variety of neoadjuvant therapies. Last, the authors demonstrate that the data obtained from mice correlated with patients: neoadjuvant treated patients showed higher TMEM score and higher MenaINV levels in tissues and in biopsy samples.

Chang and colleagues also show that paclitaxel increases TMEM numbers (tumor disseminating sites) and vascularization, as well as lung metastatic seeding and colonization of breast cancer cells. They show that paclitaxel-mediated increased metastasis is dependent on Atf3 a stress inducible gene, and the knockout of Atf3 gene was able to prevent chemotherapy induced tumor cell dissemination, lung metastatic seeding and colonization. Next, they demonstrate that Atf3 upregulation increases CCL2 expression in lungs leading to increased inflammatory macrophage infiltration and further inducing metastasis in the lung. Last, the authors used cancer patient samples to further correlate neoadjuvant chemotherapy's role in increased Atf3 expression, and in increasing tumor metastasis.

The authors comment that it is still early to remove neo-adjuvant chemotherapy from clinic; a reduction of its use in pre-operative patients with small breast tumor size could be practiced. Overall, these findings make a case for caution with the use of neoadjuvant therapies in treatment of breast cancer patients. It is still too early to predict the effect of neo-adjuvant chemotherapy on other cancer types.

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