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Editorial

# Does Chemotherapy Induce Metastases?

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Recent work on cancer metastases has raised fundamental questions about the possibility that chemotherapy promotes cancer metastases [1, 2]. In one notable paper, Karagiannis and colleagues [1] have shown in human xenograft models of breast cancer that paclitaxel, as well as cyclophosphamide with doxorubicin, all basic drugs in the adjuvant and neoadjuvant treatment of breast cancer, induce the formation of sites of tumor invasion into small blood vessels (a tumor "microenvironment" of metastasis [TMEM]) in the primary tumor; this change was associated with an increase the number of circulating tumor cells and increased lung metastases in the tumor models. Sites of tumor invasion increased in postchemotherapy tumor specimens from mice with spontaneous breast tumors induced by mouse mammary tumor virus (MMTV), as well as in mice with two different xenografts. These TMEM sites exhibit three significant changes characteristic of tumor invasion: infiltration of perivascular macrophages, increased tumor cell expression of the mammalian-enabled gene (*MENA*, known to promote metastases), and increased expression of Tie2, the angiopoietin receptor.

Furthermore, the authors provided preliminary evidence of such prometastatic changes in human tumors after chemotherapy. In 20 estrogen-receptor-positive (ER+) patients with persistence of tumor after neoadjuvant chemotherapy, the same TMEM changes were detected in post-treatment tissue samples from many of the patients.

Esserman and colleagues, who have been instrumental in proving that neoadjuvant chemotherapy improves survival in pathological complete responders [3, 4], have pondered the implications of these findings and their potential negative impact on thinking about the value of neoadjuvant chemotherapy. Multiple clinical trials indicate a benefit in time to disease recurrence and survival in patients achieving a pathological complete response to neoadjuvant chemotherapy for locally advanced breast cancer. Is it possible that those not achieving such a response will have a more rapid recurrence of disease as a result of prometastatic changes in the residual tumor? Esserman and colleagues appropriately take the conservative viewpoint that more data, particularly regarding the effects of chemotherapy at the clinical level, are needed before making any changes in current approaches to breast cancer treatment. The studies of ER+ breast cancers with persistent disease, although they show prometastatic changes after treatment, do not prove that in this subset of patients the number of metastases increased and outcomes actually worsened because of chemotherapy. We have no data to know that these patients' disease course correlated with the appearance of these prometastatic changes.

Above and beyond these immediate questions about clinical adjuvant chemotherapy, there are many other uncertainties related to these findings. Much of the work, although it provides insights into the formation of sites of tumor invasion and vascular infiltration, was done in one virally induced mouse breast cancer and two xenografts. Are these tumors representative of the spectrum of human tumors? In the case of the MMTV-induced mouse breast cancer, the tumors arose spontaneously early in the life cycle of a juvenile mouse and progressed rapidly, a history that differs from that of most human breast cancers. We are not provided information as to the level of activity of the drugs in question in these tumors; were they highly resistant to taxanes and other chemotherapy? The pathological findings in these studies require clarification. What was the tumor response to neoadjuvant therapy in these mice and patients? Are these increased numbers or proportions of prometastatic sites simply the "remnants" of a tumor site in which most tumor cells died, leaving a drug-resistant clone? Are the results pertinent to sensitive tumors? Are they consistent with the clinical experience, which indicates a clear benefit of neoadjuvant chemotherapy in predicting long-term recurrence and survival for those achieving a pathological remission [4]? And finally, are the particularly prometastatic, proangiogenic responses to taxanes a transient response to vessel injury, a known feature of taxane action [5]?

Nonetheless, these studies raise an interesting and potentially important question as to whether, in a subset of patients with prometastatic potential and drug-resistant disease, chemotherapy actually promotes metastasis and death. The authors do suggest a potential remedy, in that they show that a Tie2 inhibitor, rebastinib, blocks some, but not all, of the prometastatic changes and inhibits the increase of circulating tumor cells in the mouse and xenograft tumors. It would be of great interest to determine whether rebastinib might decrease recurrence rates and increase time to progression and survival in patients with breast cancer who receive neoadjuvant chemotherapy. An important caveat, however, is the fact that rebastinib is not a specific Tie2 inhibitor; it has multikinase specificity (CDKs and BCR-ABL kinase) and is currently in trial against chronic myelogenous leukemia [5, 6].

Until we have these results and a better understanding of the underlying biology, there is ample reason to continue the routine use of neoadjuvant chemotherapy in breast cancer.

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## References


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**For Further Reading:**

Paula Cabrera-Galeana, Wendy Muñoz-Montaño, Fernando Lara-Medin et al. Ki67 Changes Identify Worse Outcomes in Residual Breast Cancer Tumors After Neoadjuvant Chemotherapy. ***The Oncologist***; published Online First on February 28, 2018.

**Implications for Practice:**

This study evaluates the change in Ki67 percentage before and after neoadjuvant chemotherapy (NAC) and its relationship with survival outcomes in patients with breast cancer who did not achieve complete pathological response (pCR). These patients, a heterogeneous group with diverse prognoses that cannot be treated using a single algorithm, pose a challenge to clinicians. This study identified a subgroup of these patients with a poor prognosis, those with luminal B-like tumors without a Ki67 decrease after NAC, thus justifying the introduction of new therapeutic strategies for patients who already present a favorable prognosis (luminal B-like with Ki67 decrease).