

Does Chemotherapy Really Cure Breast Cancer?

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Chemotherapy before or after surgery is the standard of care for patients with breast cancers. Dozens of studies suggest that chemotherapy reduces the risk of recurrence and improves the survival of women with breast cancer. However, one cannot deny that chemotherapy is also a toxic, debilitating treatment, and chemotherapeutic agents like the most widely-used agents anthracyclines and taxanes are highly effective at killing cells [1]. The former work by damaging cellular DNA, while the latter disrupt microtubule function, and they harm healthy cells as well as cancer cells. To some extent, chemotherapeutic agents are intrinsically carcinogenic; there is a possibility that normal cells can be transformed into cancer cells, and cancer cells can become more malignant.

Our previous studies clearly demonstrated such malignant transformation [2, 3]. In order to construct a chemoresistant breast cancer cell line, we challenged MCF-7 cells with stepwise increasing concentrations of adriamycin or paclitaxel over 8 months, and found that tremendous changes occurred. The transformed MCF-7 cells became very resistant to different types of chemotherapeutic agents including adriamycin, paclitaxel, fluorouracil, and tamoxifen. At the same time, the

transformed MCF-7 cells became more metastatic. Therefore, this evidence directly indicates inevitable collateral damage from chemotherapy, raising the possibility that it makes the situation worse by initiating new cancers and enhancing malignancy.

The main reason for this drawback of chemotherapy is that it actually exerts strong selective pressure on both healthy and cancer cells, but cancer cells have evolved hundreds of mutations and epigenetic changes to cope with harsher cellular environments, which then selectively kill the weaker healthy cells and the weaker cancer cells, leaving the stronger ones. Such a selection process therefore creates the conditions for the thriving of malignant and more chemoresistant cancer cells.

The chemotherapy-proof malignant and more chemoresistant cancer cells are believed to be made up of Cancer Stem Cells (CSCs). These CSCs are usually quiescent, in contrast to their neighboring rapidly-dividing normal cancer cells, so they are less affected by most chemotherapeutic agents that target rapidly-dividing cells [4]. Furthermore, most CSCs are known to highly express drug-resistance related proteins, such as cellular transporters that can pump out chemotherapeutic agents [5], as well as proteins involved in resistance to apoptosis [6]. Therefore, these advantages enable the CSCs to stand up against the harsh toxicity of chemotherapy. In addition, CSCs are most commonly found in regions with dense blood vessels, which on the one hand provide protective shelter for CSCs, but on the other hand provide an easy route for CSCs to escape from an unfavorable

micro-environment with high concentrations of chemotherapeutic agents. During treatment, chemotherapy first plays a role in selecting for CSCs. Then chemotherapy activates quiescent CSCs by killing the surrounding normal cancer cells, which release signals to CSCs that trigger self-renewing tumorigenesis [7]. Finally, CSCs escape from the blood vessels to distant organs as metastatic tumors.

These observations mean that we should take another look at the benefits of chemotherapy, but does not mean it should be abandoned. Acknowledging a problem stimulates the search for solutions. Increasing numbers of new drugs that are more toxic to cancer cells while doing less harm to normal healthy cells are being developed; also agents that the activation signals to CSCs are being sought. We hope that in the near future, cancer can be cured as a result of deeper understanding.

References

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