Editorial

Postoperative capecitabine in breast cancer neoadjuvant failures

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Comment on: Masuda N, Lee SJ, Ohtani S, *et al*. Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy. N Engl J Med 2017;376:2147-59.

Submitted Oct 16, 2017. Accepted for publication Oct 24, 2017.
doi: 10.21037/tcr.2017.10.52
View this article at: http://dx.doi.org/10.21037/tcr.2017.10.52

In the 1st June 2017 issue of *New England Journal of Medicine*, Masuda *et al.* presented important new findings on capecitabine in HER2-negative breast cancer (1). All patients received standard neoadjuvant chemotherapy treatment before surgery with an anthracycline or a taxane, or both. Masuda *et al.* gave oral capecitabine, 1,250 mg/m^2 twice daily on days 1 to 14, nothing days 15 to 21, for 6 to 8 cycles after surgical resection to those whose surgical tissue showed residual invasive breast cancer.

Of the ~800 patients studied (half given capecitabine), 40% had stage IIIA or IIIB breast cancer, and 32% had triple-negative breast cancer. About 83% of the capecitabine group versus 74% of the control group were without recurrence 3 years, 74% of the capecitabine versus 68% of control group were alive and recurrence free at 5 years. Hormone, receptor positive patients did not benefit from adjuvant capecitabine. Triple-negative patients fared better than expected, 83% alive and recurrence free at 3 years compared to control 74%.

Future directions: like many important studies, Masuda *et al.* answered one question—yes, triple negative post-neoadjuvant, post-surgery breast cancer patients with evidence of invasive breast cancer cells on surgical tissue benefit a little from 6 to 8 cycles of capecitabine. But in answering one question, further questions are raised. Some crucial questions about best use of neoadjuvant capecitabine raised by Masuda *et al.*'s work are:

(I) To what extent did the presence (74%) or absence of hand-foot syndrome influence outcome? In erlotinib (a HER1 inhibitor) treatment, development of rash confers clear survival advantage in non-small cell cancer (2) and in multiple other cancers (3), leading some to suggest titrating erlotinib to rash. Can Masuda *et al.* retrospectively find a similar relationship to capecitabine induced hand-foot syndrome? A 2012 breast cancer study of capecitabine induced hand-foot syndrome indicates this is indeed predictive of longer survival (4) as in erlotinib rash;

(II) What were the treatment(s) employed for hand-foot syndrome? Topical emollients, corticosteroids, nicotine patch, vitamin E, pyridoxine, and cyclooxygenase inhibitors are commonly used (5). Were any of these used? Were they associated with better or worse survival?

(III) What was the differential survival in those developing neutropenia (6%) versus those not?

(IV) Did the time delay after surgery before starting capecitabine influence outcome?

(V) Were there changes in hormone receptor or HER2 status after neoadjuvant capecitabine, as have been shown by others? (6). It would be helpful to know if receptor status change rate was different in capecitabine versus control groups;

(VI) Did change in circulating tumor cells (CTC) during or after capecitabine relate to outcome? Others have shown that a decrease in CTC in metastatic breast cancer treated with docetaxel and capecitabine had a better prognosis than those not showing a decrease (7). In that study 9% had an increase in CTC under treatment. Does that portend a worse prognosis? Was CTC related to hand-foot syndrome or neutropenia?

(VII) Was there any effect of ancillary medicines, considering that others have shown these can change breast cancer prognosis, particularly angiotensin inhibitors (8), beta blockers (9) or statins on outcome or capecitabine effectiveness

compared to control? We might well expect these to enhance capecitabine effect (10,11).

Answers to the many of these questions raised by the work of Masuda *et al.* will improve effectiveness and further advance capecitabine's role in breast cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor San-Gang Wu (Department of Radiation Oncology, Xiamen Cancer Center, The First Affiliated Hospital of Xiamen University, Xiamen, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2017.10.52). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kast RE. Postoperative capecitabine in breast cancer neoadjuvant failures. Transl Cancer Res 2017;6(Suppl 9):S1446-S1447. doi: 10.21037/tcr.2017.10.52

