Beyond convention in treatment of metastatic breast cancer—rediscover overall survival

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Abstract: The Holy Grail of palliative chemotherapy in metastatic breast cancer should always be a meaningful extension of overall survival (OS). While an improvement in OS remains a sine qua non in clinical trials for many tumour groups, progression-free survival (PFS) has replaced OS as the primary end-point in most clinical trials for metastatic breast cancer. The reasons for forgoing OS in metastatic breast cancer trials are many. Chief amongst these would be the confounding effect of additional lines of treatment post progression following the study drug abrogating any inherent improvement in OS. PFS has been looked upon as a more sensitive endpoint than OS in detecting the potential benefit of a new treatment. An adequately powered trial based on PFS as the primary end-point requires a smaller patient number and a shorter follow-up period. Interestingly, the approval of the new anti-tubulin molecule eribulin in 2012 for use in pre-treated metastatic breast cancer was based on improvement in OS. This was followed by the approval of pertuzumab and T-DM1, though based on improvement in PFS, both demonstrated significant improvement in OS. These recent developments showed that OS remains a reachable end-point in many scenarios.

Keywords: Metastatic breast cancer; progression-free survival (PFS); overall survival (OS); clinical trial; palliative chemotherapy

Submitted Sep 14, 2014. Accepted for publication Oct 13, 2014.
doi: 10.3978/j.issn.2218-676X.2014.11.02
View this article at: http://dx.doi.org/10.3978/j.issn.2218-676X.2014.11.02

The Holy Grail of palliative chemotherapy in metastatic breast cancer should always be a meaningful extension of overall survival (OS).

While an improvement in overall survival remains a *sine qua non* in clinical trials for many tumour groups, such as advanced lung cancer, the breast cancer medical community has, for most intents and purposes, given up OS improvement as an unachievable pipe dream.

The reasons for forgoing OS in metastatic breast cancer trials are many. Chief amongst these would be the confounding effect of additional lines of treatment post progression following the study drug. Ethical considerations often mandate a crossover design allowing patients receiving standard treatment to also receive the study drug on progression of disease, thereby, potentially abrogating any inherent improvement in OS.

The hurdle for proving a statistically significant improvement in OS in advanced breast cancer trials is particularly high given the large number of trial participants required for an adequately powered study. Typically, a 280-patient trial will be able to detect a 3-month difference in progression-free survival (PFS). For OS, the number of participants needed varies with the average survival post progression (SPP) after exposure to the trial drug. Assuming a SPP of 2 months, a trial with 80% power to detect an OS with a p value of 0.05 would be an easy step over the threshold with a mere 350 participants. A SPP of 6 months will have a higher bar, a high jump requiring 600 participants. To clear the bar for a SPP of 24 months, as is typically the case for early-line trials for advanced breast cancer, an Olympian pole vault with a 2,440-patient trial would be required (1).

Not surprisingly, PFS has been looked upon as a more sensitive endpoint than OS in detecting the potential benefit of a new treatment. Further, the smaller patient number and a shorter follow-up period are important advantages that expedited the availability of useful treatment to patients of need.

All approvals for new drugs indicated in metastatic breast cancer granted by the Food and Drug Administration of

the United States (FDA) over the last decade hinged on the improvement in PFS or time-to-progression (TTP), with the notable exception of eribulin.

However, the use of PFS has also resulted in the fiasco of the enthusiastic approval and subsequent disappointing withdrawal of the indication for the use of bevacizumab in metastatic breast cancer by the FDA. The clinically meaningful PFS improvement of close to 6 months shown in the pivotal E2100 trial (2) with the addition of bevacizumab to standard chemotherapy proved ephemeral and largely evaporated in the follow-up AVADO (3) and RIBBON-1 (4) trials. OS was neither demonstrated in any of these trials nor in a subsequent meta-analysis. The biggest pitfall of using PFS as a surrogate for OS in advanced breast is that the relationship between the two is tenuous at best. While the strong correlation between the 3-year disease-free survival (DFS) and OS in adjuvant trials in early-stage colorectal cancer (5) justify the shortcut of using DFS as a surrogate for OS, the same cannot be said of the relationship between PFS and OS in advanced breast cancer where no discernable correlation exists (5).

There are stunts and manipulations that we, as oncologists, may pull off to indirectly prove that we are indeed doing good and extending the lives of our patients with advanced breast cancer.

One such manipulation would be to exclude patients who crossed over from the standard arm to the experimental arm in the statistical analysis. For instance, in the EGF100151 trial (6) evaluating the addition of lapatinib to capecitabine in Her2 positive advanced breast cancer following progression on trastuzumab-based therapy, the exclusion of 36 subjects who crossed from the standard capecitabine arm to the combination arm would yield a statistically significant improvement in OS of the combination over the standard arm where there was none in the primary intention-to-treat analysis. While tempting, such manipulation breaks randomization and introduces biases in the analysis.

Yet another approach is to take a step back, and view the trend in advanced breast cancer OS over an extended longitudinal time-span as Andre F has done in his *tour d'horizon* showing an improvement in OS of the period 1994-2000 over 1987-1993 (7).

Is the conduct of a clinical trial in metastatic breast cancer with OS as an end-point now forlorn?

Interestingly, the approval of the new anti-tubulin molecule eribulin in 2012 for use in pre-treated metastatic breast cancer was based on improvement in OS in the EMBRACE trial (8).

So, why has the EMBRACE trial succeeded where other trials have stumbled?

The key lies in patient selection. We may consider patients with advanced breast cancer as belonging to two categories, that of "early" metastatic disease with little or no prior treatment and "late" metastatic disease with extensive prior chemotherapy exposure.

EMBRACE compared eribulin against treatment-of-physicians'-choice (TPC) in a heavily pretreated group of patients with advanced breast cancer who have progressed on a median of four prior lines of treatment. In a heavily pretreated group of patients, the lack of a crossover design is less of an ethical issue since many patients may not be in the condition to receive further chemotherapy post progression. The fewer subsequent treatment options and shorter survival post-progression (SPP) also imply less interference by confounders on OS.

When eribulin was brought forward in the palliative chemotherapy pecking order and studied in breast cancer patients who received no more than two lines of chemotherapy in the advanced setting in the Study 301 (9), the OS over capecitabine was just shy of statistical significance, proving once again, that the tasks of proving an OS advantage in "early" versus "late" metastatic breast cancer present different levels of difficulty.

Deeper analysis of the data from Study 301, however, offers insights into another potential group of breast cancer patients, other than those with "late" metastatic disease, where demonstration of OS may be more realizable: triple negative breast cancers.

Advanced triple negative breast cancers share may characteristics with "late" metastatic breast cancers. The median OS for advanced breast cancer as a whole is between 2 to 3 years. That for triple negative breast cancer is in the ballpark of one-and-a-half to 2 years. While it is hardly unusual for the average advanced breast cancer patient to receive six or seven lines of palliative chemotherapy, triple negative cases typically only receive three to four lines.

A few recent trials, however, appear to fly in the face of the argument that OS improvement can only be demonstrated in "late" metastatic breast cancer. The two pivotal trials leading to the approval of pertuzumab and T-DM1 (ado-trastuzumab emtansine), though based on improvement in PFS, both demonstrated significant improvement in OS. The CLEOPATRA trial (10) looking at the addition of pertuzumab to trastuzumab and docetaxel is a first-line trial. The EMILIA trial (11) pitting T-DM1 against lapatinib and capecitabine is a second line trial.

In a sense, this is *déjà vu*.

I have often looked back with nostalgia to the pivotal Slamon

trial (12) in 2001 showing, for the first time, an OS benefit in the use of trastuzumab in HER2 positive metastatic breast cancer.

These developments, past and recent, show us the way forward. We need to identify driving mutations and design effective means to block them, as in the case of Her2.

If we succeed in this task, *touché*, we can afford to be ambitious, and design trials with OS as the primary endpoint.

I welcome the return of the era of OS.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research* for the series "Breast Cancer". The article did not undergo external peer review.

Conflicts of Interest: The author is on the advisory board of Roche. The author declares no conflict of interest.

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: Wong SW. Beyond convention in treatment of metastatic breast cancer—rediscover overall survival. Transl Cancer Res 2014;3(6):552-554. doi: 10.3978/j.issn.2218-676X.2014.11.02