

Letter to the Editor

The evolving role of pathologic complete response in breast cancer

DOI: 10.4103/sajc.sajc_67_19

Dear Editor,

The concept of pathologic complete response (pCR) has been an enigmatic one, often at the center of much debate and controversy. While most researchers would agree that the absence of residual invasive carcinoma in the breast and axilla is imperative in defining pCR, the impact of residual *in situ* tumor is still debated. The current AJCC 8th Edition defines pCR as the absence of any residual invasive carcinoma in the breast/axilla/lymph vessels. The presence of *in situ* tumor in the absence of invasive carcinoma still constitutes a pCR.^[1]

From the early studies onward, pCR showed great promise in its ability to predict outcomes after chemotherapy. This association was strongest in aggressive biology tumors, such as triple-negative and HER2-positive cancers.^[2] Researchers surmised that pCR could potentially be a surrogate marker for survival. Based on its ability to improve pCR rates,^[3] pertuzumab was the first drug to receive accelerated approval

from the Food and Drug Administration in 2013. The corresponding adjuvant trial (APHINITY) demonstrated only a marginal improvement in disease-free survival (94.1% vs. 93.2%, $P = 0.045$) in its early analysis, and further maturing of data is awaited. Along similar lines, addition of lapatinib improved pCR rates significantly; however, in the adjuvant setting, it failed to impact survival outcomes.^[4,5] The CTNeoBC meta-analysis^[6] funded by the US-FDA confirmed the prognostic value of pCR, especially in aggressive tumor subtypes; however, it could not validate pCR as a surrogate endpoint for survival.

Following this, pCR continued to simmer for a while and found its clinical application in its ability to prognosticate aggressive subtypes. However, the recent turn of events, specifically the CREATE-X^[7] and KATHERINE^[8] trials, has demonstrated, a hitherto unexplored, predictive capability of pCR. The CREATE-X study suggested a survival benefit with the addition of capecitabine, in women with triple-negative breast cancer, with residual disease post-neoadjuvant chemotherapy (NACT). Likewise, the early analysis of KATHERINE points toward a benefit in invasive disease-free survival with Trastuzumab emtansine over trastuzumab, in HER2-positive breast cancers with residual disease post-NACT. In both these studies, pCR, or more specifically, the lack of it, was used as a marker to tailor adjuvant therapy, with improved outcomes.

Since its inception, the role of pCR is now entering an exciting phase. It may lack the ability to be a surrogate marker for survival on the scale of a clinical trial, but it does remain a crucial marker for prognosis on an individual patient level and is an emerging predictive marker for tailoring adjuvant therapy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Nisha Hariharan, T. Subramanyeshwar Rao

Department of Surgical Oncology, Basavarakam Indo American Cancer Hospital and Research Institute, Hyderabad, Telangana, India

Correspondence to: Dr. Nisha Hariharan,
E-mail: dr.nishahariharan@gmail.com

References

1. Giuliano AE, Edge SB, Hortobagyi GN. *Ann Surg Oncol* 2018;25:1783.
2. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, *et al.* Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. *J Clin Oncol* 2012;30:1796-804.
3. Gianni L, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, *et al.* Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012;13:25-32.
4. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, *et al.* Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): A randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012;379:633-40.
5. Piccart-Gebhart M, Holmes E, Baselga J, de Azambuja E, Dueck AC, Viale G, *et al.* Adjuvant lapatinib and trastuzumab for early human epidermal growth factor receptor 2-positive breast cancer: Results from the randomized phase III adjuvant lapatinib and/or trastuzumab treatment optimization trial. *J Clin Oncol* 2016;34:1034-42.
6. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, *et al.* Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. *Lancet* 2014;384:164-72.
7. Masuda N, Lee SJ, Ohtani S, Im YH, Lee ES, Yokota I, *et al.* Adjuvant capecitabine for breast cancer after preoperative chemotherapy. *N Engl J Med* 2017;376:2147-59.
8. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, *et al.* Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med* 2019;380:617-28.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

How to cite this article: Hariharan N, Rao TS. The evolving role of pathologic complete response in breast cancer. *South Asian J Cancer* 2019;8:210-1.

© 2019 The South Asian Journal of Cancer | Published by Wolters Kluwer - Medknow