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Pathological complete response in breast cancer patients receiving neoadjuvant chemotherapy

The achievement of a complete pathological response to neoadjuvant chemotherapy (pCR, i.e. complete disappearance of invasive tumor cells from the breast and axillary lymph-nodes) has been recognized as a favorable prognostic factor in patients with operable breast cancer for a long time. [1] By accomplishing a large, individual-patient data meta-analysis of 12 randomized trials of neoadjuvant chemotherapy (NAC) Patricia Cortazar a colleagues sought, among other things, to refine the prognostic value of pCR according to the biological heterogeneity of breast cancer [2]. One of Cortazar's findings was that patients achieving pathological complete remission (pCR) as a result of NAC experienced improved event-free survival (EFS), regardless of the biological subtype of their breast cancer. This was observed, *inter alia,* both in hormone-receptor-positive, HER2-negative and well or moderately well differentiated (histological Grade 1 and 2) tumors (herewith defined as "Luminal A"), and in hormone-receptor-positive and HER2 positive tumors (herewith defined as "HER2-luminal"), although in the formers the upper value of 95% confidence interval (C.I.) fell shortly beyond the equivalence value (hazard ratio HR), 0.63, 95% C.I. 0.38–1.04).

We noted that about a half, 6377 to be exact, of patients studied in this meta-analysis came from studies conducted by German Investigators. When these patients were separately analyzed in a previous work published by Von Minckwitz in 2012 [3], no prognostic role for pCR was observed in both Luminal A and HER2-luminal tumors. These discrepant findings suggest two potential critical issues with this meta-analysis. The first one is heterogeneity of criteria to classify patients between the 7 German studies and the others. In fact, an analysis of one of the non-German studies considered in the meta-analysis, the EORTC 10994/BIG 1-00, found a consistent EFR benefit in patients achieving pCR across all the subtypes of breast cancer (including Luminal A and HER2-luminal), with HRs ranging from 0.55 to 0.41 [4]. The second issue could be reliance on peripheral assessment of ER, PgR and HER2 to stratify tumors into different subgroups that are reminiscent of the molecularly defined intrinsic subtypes. Immunohistochemical subtyping is acceptable to guide decision making provided (and to the extent) that assessment of ER, PgR and HER2 is conducted in appropriate technical contests [5]. The problem of discrepancies between peripheral and central laboratory assessment of breast cancer biomarkers is very well known and is a potential bias in any analysis based on patients from multicenter clinical studies, if no centralized revision is performed [6–8]. To cite just one of several examples, about one quarter of peripherally defined HER2-positive patients enrolled in the German study GeparQuattro could not be confirmed as such by centralized revision [9]. Therefore, we believe that the prognostic role of pCR in the context of the biological heterogeneity of breast cancer needs to be explored with caution and strict methodology before drawing conclusions that could critically affect trial design and interpretation.

On a different perspective, Cortazar's meta-analysis shows that patients achieving pCR can expect to have an excellent prognosis, yet about 35–40% of them experience disease relapse and about 15% die during follow-up (Fig. 2A and B of the paper). This is consistent with a number of studies and appears to be unrelated to the type and length of neo-adjuvant therapy received [1]. In the NOAH study [10], a focus was put on those patients achieving pCR but suffering subsequent unfavorable outcome. In this study, patients were randomly assigned to receive NAC alone or with 1 year trastuzumab started concurrently with NAC and continued after surgery. Of note, patients achieving pCR in the NAC alone arm showed a worse EFS as compared to patients achieving pCR with NAC and trastuzumab (HR 0.29, 95% CI 0.11–0.78, $p = 0.0135$). NOAH's authors were aware of this result and raised the question as to whether pCR may be considered as a plain binary, yes-or-no indicator as regards prognosis, or whether other factors may play a role as well. Since Cortazar's meta-analysis considers a total of 1989 HER2-positive patients, out of which only one half were treated with adjuvant trastuzumab, we understand that the data available in that meta-analysis could be used to seek confirmation on a broader population of the above NOAH's findings (which is based on 78 patients achieving pCR). More importantly, if this proves true, data grounding Cortazar's meta-analysis would be greatly helpful in investigating the biological background of this result, and to understand whether it just depends on underlying misclassification of certain patients as pCR achievers, or whether it may be an indicator that pCR has a different biological significance depending on the type of treatment applied (neo-adjuvant chemotherapy and/or targeted therapy).

Authors contribution

Filippo Montemurro wrote the manuscript and approved the final version.

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Letter to the Editor

Dear Editor,

Szychta et al. (2013) published an interesting article: "Breast reconstruction with the denervated latissimus dorsi musculocutaneous flap" [1]. They concluded that division of the thoracodorsal nerve is useful to minimize unnatural animation of the reconstructioned breast. Our histological, immunohistochemical and MRI data showed that the volume and consistency of the flap remains more or less the same regardless the nerve is cut or not [2]. On this basis, both cutting and saving the nerve is justified. The significance of the innervation has to be assessed together with the decision of how to deal with the humeral insertion of the LD muscle. In our study, it was completely transected. If both ends of the muscle are transected and the nerve saved, muscle loses both points of attachment and therefore the muscle activity can no longer cause major movement. If the nerve is saved and the muscle insertion is not transected, muscle contraction may cause a discomforting movement of the flap towards the axilla. Then the nerve is recommended to be cut. It would be interesting to know how Szychta et al. (2013) treat the humeral insertion of the LD muscle.

Conflict of interest statement

The author has not a financial interest to declare in relation to the content of this letter to the editor.

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