The risk of taking the part by the whole

Triple-negative (TN) breast cancer is a challenge in daily oncology practice, and we have read with great interest the article 'Platinum-based chemotherapy in triple-negative breast cancer' by Sirohi et al. [1].
Patients with TN tumors do not benefit from hormonal therapy or trastuzumab, two of the current mainstays in the systemic treatment of breast cancer. Recently, the role of a third one, anthracyclines, has been questioned after the discovery of the lack of overexpression/amplification of topoisomerase II alpha, in most TN [2]. All these compel us to look for new treatment strategies.

But we must be cautious because TN and basal-like (BL) are not synonymous, as frequently assumed. TN encompasses a heterogeneous set of tumors, with different pathological characteristics, clinical behaviors and presumably different etiologies. In fact, gene microarray analyses have demonstrated that BL represents 70% of TN, but luminal A and B, Normal-like and erbB2+ tumors are found within the other 30% [3]. In addition, not all BL are TN because ~15% of BL express HER2 and up to 35% express ER. [4]. In fact, TN includes a non-BL subgroup of tumors that unlike BL do not respond to neo-adjuvant chemotherapy but, at the same time, have a better prognosis [5]. It also seems clear that, within TN, tumors that express basal markers such as EGFR or basal cytokeratins belong to a clinically different subgroup with worse prognosis, regardless of their receptor status.

Reports like this one, in which TN are referred as BL, a mixture of BL and non-BL tumors, are actually included, while those BL with ER+ are excluded, introducing significant histological and clinical heterogeneity. This is important because only BL, and not TN as a whole, is the group that exhibits a more aggressive course with a different metastatic pattern and shorter survival [6]. There are several lines of evidence suggesting a link between BL and BRCA1 deficiency [6, 7]. Among other many functions, BRCA1 repairs double-strand breaks such as those induced by platinum, and BL have shown an increased sensitivity to these compounds in cell cultures. Nevertheless, BRCA1 is probably not involved in the pathogenesis of other breast cancer subgroups, which also can be TN, and they do not benefit from the use of these drugs.

The conclusions of this study [1] could lead us to discard a potentially useful therapeutic weapon by the erroneous consideration that the response of TN to platinum salts is minimal. In our opinion, the modest statistical significance obtained could be due to the fact that the benefit obtained from the platinum use in BL is diluted by the inclusion of a heterogeneous group of tumors, with a wide range of sensitivity to these drugs but with the common characteristic of being TN. In addition, the possible platinum effect could be masked by the use of schemes including anthracyclines [2].

In order to assess the actual effectiveness of platinum salts, we think not only a bigger prospective study is needed but patient selection must be improved. BL tumors can be selected by microarrays or by a rational combination of morphology and immunohistochemistry (including ER, PR, HER2, and also cytokeratins CK5/6 and/or CK17 and EGRF), but we cannot assume that ER−, PR−, and HER2− are enough to define a tumor as BL [3, 4, 6].

For these reasons, we would like to call for caution in the interpretation of this and most of the ongoing clinical trials that explore the therapeutic options for TN, which equates these tumors with BL. While on the one hand, efforts are currently being directed to tailor treatments to the molecular profile of each tumor, on the other hand, a mistake is made when TN is considered a homogeneous tumor group. In other words, the part should not be taken by the whole.

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references


doi:10.1093/annonc/mdn598
Published online 2 September 2008