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Editorial: Triple-negative Breast Cancer.

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Triple-negative breast cancer, usually defined as an invasive cancer lacking expression in estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor type 2 (HER2) as detected mainly by immunohistochemical methods, is of interest firstly because systemic treatment options for this cancer are currently limited. Triple-negative cancers are unlikely to respond to hormonal treatment, and therapies targeting HER2 receptors are probably of no value. The only systemic treatment available is some form of combination cytotoxic chemotherapy. Secondly, triple-negative cancers are often thought to have an unfavorable prognosis.[1-3]

The first interesting aspect of triple-negative breast cancer, i.e. the currently limited systemic treatment options, is being actively investigated in many research centers. However, one difficulty must be addressed before any major progress towards finding novel treatments specifically targeted for these cancers can be made. The difficulty is best phrased as a question: what exactly is a triple-negative breast cancer? More precisely, what are the molecular-genetic characteristics of these cancers? This characterization would define the triple-negative category, help establish whether heterogeneity at the genetic level exists for these tumors, and suggest promising molecular signaling pathways which could be targeted for treatment. (We are assuming that the lowest meaningful level of description is molecular-genetic, and this level of description defines the phenotype almost completely).

It has been recognized early on that triple-negative breast cancer is at best a pragmatic descriptive term for a variety of cancers with differing biological behavior, and no known set of unique genetic signatures corresponds exactly to this description. For example, the currently accepted genetic profiling of breast cancers, classifying breast cancers into five broad categories, provides one subgroup - the basal-like tumors - which largely overlaps with the triple-negative phenotype. But, although approximately 80% of all triple-negative tumors are basal-like, up to 40% of all basal-like tumors are not triple-negative.[2] To complicate matters, many triple-negative tumors also have BRCA1 (and to a lesser extent, BRCA2) gene mutations as well.[3] Even the basal-like tumors themselves are not genetically and clinically homogeneous.

Triple-negative and basal-like breast cancer with overexpression of “basal-like features” on immunohistochemical staining - either the cytokeratins (CK5/6/14/17)[2,3] or epidermal growth factor receptor (EGFR or HER1) expression or both - is known to have an

especially poor prognosis. This subgroup, also known as the "core basal" phenotype,[2] is, in part, likely to consist of those cancers with poor response to conventional chemotherapy, or those which relapse early after treatment. These cancers are also likely to have BRCA1 gene mutation. In contrast, triple negative cancers with negative staining for cytokeratin and EGFR (the "quintuple-negative") have a good prognosis[2] and probably respond better to chemotherapy. In fact, they may respond well to anthracycline-based regimen and taxanes to an extent even greater than that seen in the ER-positive (luminal-type) tumors, when these chemotherapeutic agents are used in the neoadjuvant setting.[1-3]

Thus, although the triple-negative phenotype is heterogeneous with respect to molecular-genetic and clinical aspects, and cannot currently be (or probably ever need to be) uniquely characterized, it is possible to identify certain subgroups in greater need of novel therapies, by using genetic analysis and immunohistochemical methods. These are the triple-negative, basal-like cancers with BRCA gene mutations and expression of basal cytokeratins and EGFR. Some progress has been made in the treatment of these cancers. Although it is too early to be certain, it seems that, because of the defect in the BRCA1 gene, platinum-based chemotherapy might be useful.[2,3] Bevacizumab, an antibody used to inhibit angiogenesis, might also be beneficial in the neoadjuvant setting but only in combination with appropriate chemotherapy.[4,5] The US FDA, however, have found the benefits of bevacizumab to be insufficient for treating metastatic breast cancer.[6] Newer agents such as the PARP inhibitors, targeting the enzyme poly (adenosine diphosphate-ribose) polymerase (PARP) used for repairing DNA damage, might be more promising.[7,8] Therapies targeting EGFR might be possible (e.g. cetuximab), but limited data suggest that triple-negative tumors might be resistant to such therapies.[2]

"Triple negative" as a descriptor might be too non-specific and too irrelevant clinically for it to survive the decade after newer and effective therapeutic agents become available for some of the cancers falling under this umbrella term.[2] In the meantime, it is still useful in many clinical settings because more detailed characterizations (extensive use of immunohistochemical staining, molecular-genetic profiling, genetic mutation mapping, etc.) are simply too expensive or impractical. A possible but perhaps controversial way to screen triple-negative cancers for further targeted treatments, when they become available, is to provide neoadjuvant chemotherapy routinely for these cancers, perhaps at more advanced stages (e.g. stage IIb or higher). Those that show minimal, or even only partial, response should be considered for second-line chemotherapy or targeted therapy before or after surgery.

The second interesting aspect of triple-negative breast cancer, actually strongly related to the first, is its apparently poor prognosis. We have already discussed this briefly in therapeutic terms. However, poor prognosis in terms of disease recurrence and cancer-related death might not be easy to show in a clinical study. One such study is presented in the current issue of Ramathibodi Medical Journal.

The present study retrospectively compared 256 breast cancer patients having non-triple negative phenotype, with 54 patients having triple-negative phenotype. The outcome was the disease-free probability (not disease-free survival) after treatment. These patients represented a subset of consecutive breast cancer patients operated on during the years 2002 to 2006, a subset with complete data on ER, PR and HER2 expressions. Consequently, substantial selection bias might exist but its impact is unknown. Despite this limitation, certain features of the triple-negative group, compared with those of the non-triple negative, as detailed in the present paper, were consistent with previous studies.

Triple-negative cancers are associated with younger age, tend to be larger, have higher histologic grade, possibly with smaller likelihood of axillary metastasis, and show no clear association between the size of the primary tumor and presence of axillary metastasis.[1-3] Such were also the findings of the present study, although some of these trends were not statistically significant. What might be surprising in light of all previous discussions was the similar disease-free probability between the triple and non-triple negative groups. It seems as if triple-negative tumors have rather good (or non-triple negative tumors have rather bad) prognosis after all.

Without any information on the mixture of the various immunohistochemical phenotypes in the two groups,[2,9] the finding of no significant difference in recurrence should not necessarily come to as a surprise. As discussed in the paper, the finding could have been due to "a fortuitous mixture of good prognosis ... and bad prognosis ... tumors" in both groups. That is, there might be a high proportion of chemoresponsive patients in the triple-negative group, thus reducing their recurrence rate, and at the same time, there might be a sufficiently high proportion of HER2-positive patients in the non-triple negative group, increasing their recurrence rate, such that the comparison of the recurrence rates in both groups did not reveal any apparent difference. What the authors should have done, therefore, was to show evidence in the data that this was indeed the case, but alas they did not. This highlights the problem with many observational clinical studies of cancer prognosis: a large variation in patient population and methodology among the studies,[10] many of which do not sufficiently resemble one another, and often not well characterized, leading to poor generalizability.

On a more positive note, if it were true that many patients in our institution with triple-negative breast cancer are chemoresponsive, we have a potentially large number of subjects on whom to perform molecular-genetic profiling to show how and why these patients are so favorable. This could help in distinguishing from those with a potentially poor response to chemotherapy, and hence to better tailor our treatment options to patients with triple-negative breast cancer. There should be no need to screen triple-negative cancer patients with neoadjuvant chemotherapy; predicting beneficial effects of so-called targeted therapy should be made before any treatment, and if predicted to be so, targeted therapy can even be given up front.

In conclusion, triple-negative breast cancers are of current interest, and probably will be so in the near future. Therapeutically relevant subgroups of these cancers are increasingly being recognized, and therapies are being developed to deal with them. These novel therapies are not targeting triple-negative tumors uniquely, but rather targeting the more unfavorable subgroups. Some triple-negative cancers have very good prognosis if pathologically complete response can be obtained after chemotherapy. At the present time neoadjuvant chemotherapy provides a way to distinguish favorable from unfavorable subgroups.

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