Since the start of the 1990s, molecular pathology has been playing an increasingly important role in cancer diagnosis and treatment. Nowhere is this role more evident than in the case of breast cancer. Traditional criteria such as the size and histologic grade of the primary tumour and the number of positive axillary lymph nodes have been the major focus for many years. Today, immunohistochemical tests and other molecular and cytogenetic tests are usually necessary for an exact diagnosis and for assessment of the degree of invasiveness. Moreover, those tests are now essential for an accurate evaluation of prognosis and initiation of the appropriate treatment.

Since 2000, hypothesis-free gene-expression studies of breast cancer have identified 5 different “intrinsic” molecular subtypes having prognostic value, initially defined as luminal A, luminal B, HER2 (human epidermal growth factor receptor 2)—positive, “normal-like,” and basal-like breast cancer. However, gene expression studies require RNA and are not routinely performed. Nevertheless, attempts have been made to approximate these intrinsic subtypes with more readily-available immunohistochemical methods (Table 1).

The triple-negative phenotype, defined as the lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression, represents approximately 12%–17% of breast cancer cases. As shown in Table 1, most basal-like breast cancers also have a triple-negative phenotype, but up to 20% express ER or overexpress HER2. Thus, the overlap is not perfect between the molecularly defined and the immunohistochemically defined breast cancer classifications.

Other molecular subtypes have also been found within triple-negative breast cancers, including a claudin-low subgroup, an interferon-rich subgroup, and even a normal breast-like subgroup, which may represent an artifact attributable to contaminating normal epithelium. Notably, 75% of breast cancers in women who carry a germline BRCA1 mutation have basal-like or triple-negative phenotypes (or both). Not surprisingly, despite the marked absence of BRCA1 somatic mutations, studies suggest that the BRCA1 pathway may be dysfunctional in at least some nonhereditary basal-like tumours. It is now clear that both the basal-like and the triple-negative breast cancers are heterogeneous subgroups that will probably be more precisely defined in the future.

Nevertheless, the actual definitions of basal-like and triple-negative breast cancer have been demonstrated to be clinically significant, in that they identify breast cancer patients with different risk factors and, importantly, different natural histories. Women who develop a basal-like breast cancer are more likely to have reached menarche at a younger age, to have had a higher body mass index during their premenopausal years, and to have had a higher parity and lower lifetime duration of breastfeeding in comparison with women without cancer. The basal-like and triple-negative phenotypes are both associated with usually aggressive high-grade invasive cancer.

**TABLE 1** Immunohistochemical phenotype of molecularly defined breast cancer subtypes

<table>
<thead>
<tr>
<th>Molecular subtype</th>
<th>ER</th>
<th>PR</th>
<th>HER2</th>
<th>CK5/6</th>
<th>EGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Luminal B</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>HER2-positive</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Basal-like</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

a For each molecular subtype, the usual immunohistochemistry pattern of staining is shown. However, some discordance exists between the molecularly and immunohistochemically defined tumour subtypes.

b Triple-negative tumours that are also CK5/6- or EGFR-positive are defined as having a “core basal phenotype,” but the inclusion of PR in this classification is of uncertain benefit.

ER = estrogen receptor; PR = progesterone receptor; CK = cytokeratin; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2.
ductal carcinomas that, of all breast cancer subtypes, are found in greater proportion in black and Hispanic women than in white women. Compared with the other subtypes, they are more likely to be larger, more likely to metastasize to lungs and brain, and less likely to metastasize to bone. Both have a natural history different from that of the other subtypes, with a characteristic sharp decrease in survival during the 3–5 years after diagnosis, and with a much lesser likelihood of distant relapse at 10 years than is seen in patients with ER-positive tumours.

In this issue of Current Oncology appears a retrospective study by Caroline Hamm and colleagues that looks at 1018 breast cancer patients diagnosed between 2000 and 2005 with a follow-up period of 8 years. The authors found that, when matched for age, stage, and treatment, women with triple-negative breast cancer could expect to have the same survival as other patients—at least during the first 3 years. Notably, in that study, 85% of patients with the triple-negative phenotype received chemotherapy. Tumour size appeared to be a major prognostic factor, although two independent studies found that there was a diminished effect of tumour size on the prognosis of patients with basal-like breast cancers, possibly because smaller basal-like breast cancers fared worse than expected, but that larger cancers had a better prognosis than larger non-basal-like breast cancers.

So what does all this mean for the oncologist?

Women with triple-negative breast cancer and most of those with basal-like phenotypes are currently treated with chemotherapy because they cannot benefit from endocrine therapy or trastuzumab. Treatment options for triple-negative breast cancer have recently been extensively reviewed. Although patients with tumours having a triple-negative phenotype experience worse outcomes as a group, adjuvant chemotherapy improves their survival to a greater extent than it does survival in patients with ER-positive tumours.

There is currently no preferred standard form of chemotherapy for patients with triple-negative or basal-like breast cancers. Anthracycline-based regimens in the adjuvant setting are associated with a benefit in relapse-free survival that is at least similar to that observed in the HER2-positive subgroup. A meta-analysis of evidence from available studies suggests that anthracycline-containing regimens are more effective than cyclophosphamide, methotrexate, and fluorouracil in triple-negative tumours; but confusingly, one retrospective trial suggests the opposite for basal-like breast cancer. The explanation for these different results is unclear, but intensive research is attempting to identify triple-negative-specific targets.

Studies of neoadjuvant chemotherapy in women with triple-negative breast cancer have demonstrated a higher incidence of complete pathologic response (pCR) than is seen in women with different subtypes of breast cancer, with an excellent outcome for all who achieve a pCR, regardless of immunohistochemical subtype. In comparisons with other subgroups, the major difference is that outcomes for women with triple-negative breast cancer who do not achieve a pCR are much more adverse than they are for women with other subtypes of breast cancer who similarly do not achieve a pCR. The addition of taxane agents (such as docetaxel or paclitaxel) to anthracycline-based regimens in the neoadjuvant and adjuvant settings, appears to confer an even greater benefit in triple-negative tumours. It seems likely that within triple-negative tumours there lies a chemosensitive molecular subgroup conferring a particularly good outcome, and it is possible that most or all of the currently-used chemotherapeutic agents would be effective for these women. Whether “mixing and matching” of any of these existing agents can improve the notably poor prognosis for women with triple-negative breast cancer who do not achieve a pCR after neoadjuvant chemotherapy is an important unresolved question.

Clinical trials assessing the use of platinating agents (such as cisplatin and carboplatin) in the treatment of triple-negative breast cancer are currently under way, based on the presumption that a dysfunctional BRCA1 pathway affecting DNA repair sensitizes cells to those agents. However, initial findings suggest that, in the neoadjuvant setting, pCR will be no easier to achieve than it is with other types of treatments. That finding contrasts with the high rates of pCR observed in women whose breast cancers carry a BRCA1 mutation. Trials looking at the benefit of epothilone (a member of a new class of microtubule-targeting agents) in the metastatic setting are ongoing, and initial results show improved response rates, progression-free survival, and overall survival.

The use of targeted therapy is also being investigated in multiple trials. In the metastatic setting, use of the anti-angiogenic agent bevacizumab has been shown to consistently improve progression-free survival in triple-negative breast cancer patients, and bevacizumab is currently being evaluated in the neoadjuvant and adjuvant settings. Poly(ADP-ribose) polymerase (PARP) inhibitors such as olaparib and iniparib were developed to target the base excision repair pathway of single-strand DNA. It has been observed that cells will be killed only if more than one of the DNA repair pathways that they rely upon are inactivated. In tumours arising in BRCA1 mutation carriers, homologous recombination is defective; however, it is functional in non-cancer cells. Adding an inhibitor of PARP knocks out the base excision repair pathway and forces the cells to use the homologous recombination pathway—and if the latter pathway is not working properly, the cells will be destroyed. Based
on the benefit observed in breast cancer patients who carry germline *BRCA1* mutations and on the expected relative deficiency in double-strand DNA repair (secondary to dysfunctional *BRCA1* pathways) in triple-negative breast cancer, therapeutic targeting of this alternative DNA repair pathway was attempted. The name “parp” has been given to the family of drugs whose mechanism of action is based on PARP inhibition.

In the metastatic setting, a phase II study looking at the addition of iniparib to gemcitabine and carboplatin has produced exciting results, with significantly increased rates of response, progression-free survival, and overall survival compared with rates achieved using chemotherapy alone in the treatment of patients with triple-negative breast cancer. Unfortunately, the recently available phase III study results did not meet the pre-specified primary goals in terms of progression-free or overall survival. Moreover, the mechanism of action of iniparib is now in question. Nevertheless, the final results of the phase III study are awaited with interest. By contrast, the use of olaparib, an oral PARP inhibitor, for the treatment of locally advanced or metastatic breast cancer in women carrying a *BRCA1* or *BRCA2* mutation was associated with an impressive overall response rate of 41%.

Surprisingly, in a phase II study that recently looked at the single-agent activity of olaparib in patients with triple-negative breast cancers, clinical response in the first 15 patients was insufficient to justify pursuing the trial. However, caution must be exercised with these preliminary findings; until the full details are published, over-interpretation of this trial is a risk.

With the identification of *PTPN12* tyrosine phosphatase protein as a tumour suppressor that is lost in 60% of triple-negative breast cancers, there is hope that new therapeutic possibilities will be uncovered. The *PTPN12* protein acts as a tumour suppressor by antagonizing key tyrosine kinase receptors such as epidermal growth factor receptor and inhibiting the tyrosine kinase receptors) impairs the tumorigenic and metastatic potential of triple-negative cancer cells.

Further insights into the molecular classification of breast cancer and the underlying molecular events at the origin of triple-negative and basal-like breast cancers is expected to lead to better patient management practices. The rapidly evolving field of molecular pathology is progressively taking its place in routine pathology practice, and it has been predicted that the molecular classification of breast tumours will eventually replace the morphology-based approach. Moreover, if specific treatments are found to be more or less effective in women carrying genetic mutations in breast cancer susceptibility genes, the need for publically-funded, rapid, and widespread testing for those genes will become of paramount importance.

**CONFLICT OF INTEREST DISCLOSURES**

WDF has received honoraria from Sanofi–Aventis.

**REFERENCES**


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