Triple-negative and basal-like breast cancer: implications for oncologists

J. Lachapelle and W.D. Foulkes†*

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 [1]. 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 I) [2].

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 I, 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 [4,5].

TABLE I Immunohistochemical phenotype of molecularly defined breast cancer subtypes

Molecular subtype	*Immunohistochemical staining*[a]				
	ER	*PR*	*HER2*	*CK5/6*[b]	*EGFR*[b]
Luminal A	+	+	–	–	–
Luminal B	+	+	+	–	–
HER2-positive	–	–	+	–	–
Basal-like	–	–	–	+	+

[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 [3].

ER = estrogen receptor; PR = progesterone receptor; CK = cytokeratin; EGFR = epidermal growth factor receptor; HER2 = human epidermal growth factor receptor 2.

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 [4,6]. 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 [7]. The basal-like and triple-negative phenotypes are both associated with usually aggressive high-grade invasive

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 [8]. 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 [9,10].

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 [6,11]. 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 [12]; but confusingly, one retrospective trial suggests the opposite for basal-like breast cancer [13]. 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 [14]. 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 [15,16]. 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 [17]. That finding contrasts with the high rates of pCR observed in women whose breast cancers carry a *BRCA1* mutation [18]. 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 [19].

The use of targeted therapy is also being investigated in multiple trials [6,11]. 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 [6]. 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 [20]. 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 "paribs" 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 [21]. Unfortunately, the recently available phase III study results did not meet the pre-specified primary goals in terms of progression-free or overall survival [22]. 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% [23].

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 [24]. 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 HER2, and experimental restoration of PTPN12 function (or inhibition of the tyrosine kinase receptors) impairs the tumorigenic and metastatic potential of triple-negative cancer cells [25,26].

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 [27]. 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

1. Sørlie T, Perou CM, Tibshirani R, *et al.* Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. *Proc Natl Acad Sci U S A* 2001;98:10869–7.
2. Tang P, Skinner KA, Hicks DG. Molecular classification of breast carcinomas by immunohistochemical analysis: are we ready? *Diagn Mol Pathol* 2009;18:125–32.
3. Tischkowitz M, Brunet JS, Bégin LR, *et al.* Use of immunohistochemical markers can refine prognosis in triple negative breast cancer. *BMC Cancer* 2007;7:134.
4. Foulkes WD, Smith IE, Reis–Filho JS. Triple-negative breast cancer. *N Engl J Med* 2010;363:1938–48.
5. Rakha E, Reis–Filho JS. Basal-like breast carcinoma: from expression profiling to routine practice. *Arch Pathol Lab Med* 2009;133:860–8.
6. Carey L, Winer E, Viale G, Cameron D, Gianni L. Triple-negative breast cancer: disease entity or title of convenience? *Nat Rev Clin Oncol* 2010;7:683–92.
7. Millikan RC, Newman B, Tse CK, *et al.* Epidemiology of basal-like breast cancer. *Breast Cancer Res Treat* 2008;109:123–39.
8. Hamm C, El-Masri M, Poliquin G, *et al.* A single-centre chart review exploring the adjusted association between breast cancer phenotype and prognosis. *Curr Oncol* 2011;18:191-196.
9. Foulkes WD, Grainge MJ, Rakha EA, Green AR, Ellis IO. Tumor size is an unreliable predictor of prognosis in basal-like breast cancers and does not correlate closely with lymph node status. *Breast Cancer Res Treat* 2009;117:199–204.
10. O'Brien KM, Cole SR, Tse CK, *et al.* Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. *Clin Cancer Res* 2010;16:6100–10.
11. Enright K, Dent R. Treatment options for triple-negative breast cancer. *Emerg Cancer Ther* 2010;1:589–606.
12. Di Leo A, Isola J, Piette F, *et al.* A meta-analysis of phase III trials evaluating the predictive value of HER2 and topoisomerase II alpha in early breast cancer patients treated with CMF or anthracycline-based adjuvant therapy [abstract 705]. *Breast Cancer Res Treat* 2008;107(suppl):24. [Available online at: www.abstracts2view.com/sabcs/view.php?nu=SABCS08L_538; cited June 21, 2011]
13. Cheang M, Chia SK, Tu D, *et al.* Anthracyclines in basal breast cancer: the NCIC-CTG trial MA.5 comparing adjuvant CMF to CEF [abstract 519]. *J Clin Oncol* 2009;27:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=65&abstractID=35150; cited June 15, 2011]
14. Liedtke C, Mazouni C, Hess KR, *et al.* Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol* 2008;26:1275–81.
15. Nahleh Z. Neoadjuvant chemotherapy for "triple negative" breast cancer: a review of current practice and future outlook. *Med Oncol* 2010;27:531–9.

16. Ellis P, Barrett–Lee P, Johnson L, *et al.* Sequential docetaxel as adjuvant chemotherapy for early breast cancer (TACT): an open-label, phase III, randomised controlled trial. *Lancet* 2009;373:1681–92.
17. Silver DP, Richardson AL, Eklund AC, *et al.* Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. *J Clin Oncol* 2010;28:1145–53.
18. Byrski T, Gronwald J, Huzarski T, *et al.* Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J Clin Oncol* 2010;28:375–9.
19. Roché H, Conte P, Perez EA, *et al*. Ixabepilone plus capecitabine in metastatic breast cancer patients with reduced performance status previously treated with anthracyclines and taxanes: a pooled analysis by performance status of efficacy and safety data from 2 phase III studies. *Breast Cancer Res Treat* 2011;125:755–65.
20. Rehman FL, Lord CJ, Ashworth A. Synthetic lethal approaches to breast cancer therapy. *Nat Rev Clin Oncol* 2010;7:718–24.
21. Drew Y, Plummer R. The emerging potential of poly(ADP–ribose) polymerase inhibitors in the treatment of breast cancer. *Curr Opin Obstet Gynecol* 2010;22:67–71.
22. Sanofi–Aventis. Sanofi-Aventis Reports Top-Line Results from Phase III Study with BSI-201 in Metastatic Triple-Negative Breast Cancer [press release]. Paris, France: Sanofi–Aventis; 2011. [Available online at: en.sanofi.com/binaries/20110127_BSI_en_tcm28-30168.pdf; cited June 15, 2011]
23. Tutt A, Robson M, Garber JE, *et al.* Oral poly(ADP–ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and advanced breast cancer: a proof-of-concept trial. *Lancet* 2010;376:235–44.
24. Gelmon KA, Hirte HW, Robidoux A, *et al.* Can we define tumors that will respond to PARP inhibitors? A phase II correlative study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer [abstract 3002]. *J Clin Oncol* 2010;28:. [Available online at: www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=74&abstractID=50240; cited June 15, 2011]
25. Sun T, Aceto N, Meerbrey KL, *et al.* Activation of multiple proto-oncogenic tyrosine kinases in breast cancer via loss of the PTPN12 phosphatase. *Cell* 2011;144:703–18.
26. Albeck JG, Brugge JS. Uncovering a tumor suppressor for triple-negative breast cancers. *Cell* 2011;144:638–40.
27. Pakkiri P, Lakhani SR, Smart CE. Current and future approach to the pathologist's assessment for targeted therapy in breast cancer. *Pathology* 2009;41:89–99.

Correspondence to: William D. Foulkes, Program in Cancer Genetics, Gerald Bronfman Centre, Department of Oncology, McGill University, 546 Pine Avenue West, Montreal, Quebec H2W 1S6.
E-mail: William.foulkes@mcgill.ca

* Department of Pathology, McGill University, Montreal, QC.
† Program in Cancer Genetics and Departments of Oncology and of Human Genetics, McGill University, Montreal, QC.