The Breast 21 (2012) 20–26

Contents lists available at SciVerse ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

Review

Triple negative breast cancer: Proposals for a pragmatic definition and implications for patient management and trial design

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ARTICLE INFO

Article history:
Received 4 July 2011
Received in revised form
2 September 2011
Accepted 4 September 2011

Keywords:
Basal-like
Breast cancer
Her2
Histopathology
Oestrogen receptor
Triple negative

ABSTRACT

In trials in triple negative breast cancer (TNBC), oestrogen and progesterone receptor negativity should be defined as < 1% positive cells. Negativity is a ratio of <2 between Her2 gene copy number and centromere of chromosome 17 or a copy number of 4 or less. In routine practice, immunohistochemistry is acceptable given stringent quality assurance. Triple negativity emerging after neoadjuvant treatment differs from primary TN and such patients should not enter TNBC trials. Patients relapsing with TN metastases should be eligible even if their primary was positive. Rare TN subtypes such as apocrine, adenoid-cystic and low-grade metaplastic tumours should be excluded. TN and basal-like (BL) signatures overlap but are not equivalent. Since the significance of basal cytokeratin or EGFR overexpression is not known and we lack validated assays, these features should not be used to subclassify TN tumours. Tissue collection in trials is mandatory so the effect on outcome of different tumour phenotypes and BRCA mutation can be explored. No prospective studies have established that TN tumours have particular sensitivity or resistance to any specific chemotherapy agent or radiation. TNBC patients should be treated according to tumour and clinical characteristics.

Introduction

The nature and implications of a triple negative (TN) phenotype – ie minimal or low expression of both oestrogen and progesterone receptors (ER and PgR) and the lack of type-2 human epidermal growth factor receptor (Her2) overexpression or gene amplification – is one of the most active areas of research and debate in breast cancer.[1–6] Triple negativity is associated with younger age at diagnosis and occurs with greater frequency in non-Caucasian, premenopausal women and those who are overweight (particularly with abdominal obesity).[7] TN cancers are more likely than other kinds of breast tumour to occur in the intervals between mammographic screening.[7] Triple negative breast cancer (TNBC) is aggressive, showing a tendency towards early metastasis and

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doi:10.1016/j.breast.2011.09.006

having a poor overall outcome despite being highly responsive to conventional chemotherapy. TN tumours have a greater tendency to metastasise to lung and brain[8] and (when compared with luminal tumours) relatively little propensity to metastasise to bone.[9] Recurrence within two-three years is relatively common, and absence of recurrence of TN tumours within five years suggests a low risk of subsequent distant metastasis.

Given the lack of hormone and growth factor receptor drug targets, non-surgical treatment options for patients with TNBC have until recently been confined to chemotherapy and radiation. Today, increased understanding of the molecular biology of TN tumours is generating a wealth of clinical trial activity. Around twenty current trials are specifically accruing TN patients for studies in the adjuvant, neoadjuvant and advanced or metastatic settings.[1]

Despite its attraction to triallists, the concept of triple negativity is not without problems. Firstly, receptor expression is not all-or-nothing; and there is no uniformly accepted cut-off point that defines its absence. Current trials therefore differ in the receptor expression thresholds below which patients must fall to qualify for entry. Secondly, as with any phenomenon categorised by exclusion, we can be reasonably sure of what TNBC is not, but not necessarily of what it is. Having excluded patients whose tumours express hormone receptors and overexpress Her2, we are left with a heterogeneous collection of cases. High grade predominates, as does an invasive ductal (not otherwise specified) origin. However, TN tumours display many different morphologies and molecular characteristics. The complexity of the field is illustrated by the relationship between the concepts of triple negativity and of basal-like (BL) breast cancer: certain authors consider these terms as virtually synonymous while others emphasise their differences.[10–14] As in many complex situations, there is a tension between seeing the picture clearly and seeing it whole. In respect of the sensitivity of TNBCs to particular classes of cytotoxics, for example, the more closely the literature is scrutinised, the less clear are the conclusions that can be drawn.

Both the recognition that hormone receptor-positive breast cancer was sensitive to endocrine treatment and the demonstration that Her 2 positive tumours responded to drugs directed at this growth factor brought major advances in care. A pressing question now is whether definition of a TN phenotype, and the development of treatments tailored to it, can bring similar progress.

Under the auspices of Eticho (European Training in Clinical Hematology and Oncology) an ad hoc but expert group of clinicians and pathologists convened in Milan in October 2010. The meeting discussed first how TNBC might best be defined pragmatically (taking into account not only the classical markers of hormone and growth factor receptor status but also possible additional molecular and clinical characteristics) and, secondly, how to apply this definition in selecting patients for clinical trials and, in the everyday clinical setting, as a guide to management. This report presents a series of proposals for further discussion.

Defining triple negativity

Hormone receptor status

There are considerable practical limitations to relevant assays. Using IHC to determine hormone receptor status, the rate of false negative or positive findings may be as high as 20%.[15] There is lack of reproducibility and variability between institutions. In the individual patient, the results obtained may reflect intratumoural heterogeneity in the expression of relevant markers; primary and metastatic deposits can differ appreciably in their receptor expression; and receptor positivity/negativity may change during tumour progression and in response to systemic therapy.

Two recent expert groups have recommended thresholds for the use of specific adjuvant therapies. The 2009 St Gallen consensus proposed endocrine therapy for patients whose tumours showed any ER staining, or “the presence of any detectable oestrogen receptor”.[16] The 2010 American Society of Clinical Oncology-College of American Pathologists (ASCO-CAP) recommendations suggest 1% as the threshold for an ER positive tumour, so as not to deny any patient a potentially helpful treatment.[15]

However, having a single threshold for hormone receptor positivity is arbitrary and confusing to clinicians and patients who cannot understand why a difference that in itself is small – but sufficient to place a patient one side of the cut-off rather than the other – should have such profound implications for treatment. The suggestion is that there be two cut-offs – a higher value above which almost everyone agrees the patient is positive, and a lower one which almost everyone agrees means negativity, leaving a grey zone in between.

We propose that – when designing clinical trials of novel agents in TNBC – ER negativity should be defined strictly as the lack of or presence of fewer than 1% positive cells, irrespective of staining intensity. When developing novel agents for TNBC, there is virtue in working with a clearly defined biological entity. In everyday clinical practice, however, a less stringent cut-off may be adopted. In the zone between 1% and 10% we look for guidance to other features of the tumour and the circumstances of the patient when deciding on the appropriateness of endocrine therapy since there is evidence of some response to endocrine manipulation in this grey zone.[17,18] In patients whose tumours have more than 10% of cells expressing ER, endocrine therapy should be offered.

The presence of PgR negativity in the definition of the triple negative patient has been questioned. Although PgR status is of independent prognostic significance in meta-analyses,[19] its lack of predictive value in the individual patient has led some to reject its inclusion, favouring instead the concept of “dual negativity”. Furthermore, perhaps because PgR expression is downstream of ER, it is rare for a particular patient to be ER negative but PgR positive. Indeed, the St Gallen group argue that such findings are largely or wholly artefactual.[16] An ER-negative but PgR positive result strongly suggests the need for repeat ER assay. For this reason alone (and despite its cost), there is merit in the simultaneous determination of ER, PgR and Her2.

For the purposes of clinical trial eligibility, PgR negativity should be defined (as for ER) as fewer than 1% positive cells, irrespective of staining intensity. In routine clinical practice, up to 10% positive cells may also be considered PgR negative. Tumours with more than 10% of cells positive for PgR should be considered positive.

Some studies have suggested that triple negative but androgen receptor-positive tumours (around 30% of TN cases) may have a better prognosis than TN androgen-negative tumours.[20,21] Androgen receptors may in the future help constitute a clinically relevant subgroup. However, current data do not justify assay of androgen receptors in clinical practice, and indeed no well-validated diagnostic antibody is available. Nevertheless, we strongly recommend that androgen receptor status should be investigated in TNBC trials, particularly since new agents targeting this receptor are being developed.

Her2 status

In a study of 24 Swedish pathology departments, each laboratory was sent a tissue microarray including eleven primary breast cancer samples for Her2 analysis. IHC showed reasonable reproducibility: for six of the eleven samples, all laboratories reported the same findings (0/1 + vs 2 + vs 3+; mean kappa value 0.77). However, reproducibility across centres was considerably higher