Triple negative breast cancer: a heterogeneous subgroup defined by what it is not

Catherine Oakman[a], Erica Moretti[a], Giulia Pacini[b], Libero Santarpia[b], Angelo Di Leo[a]

[a] *"Sandro Pitigliani" Medical Oncology Unit, Hospital of Prato, Istituto Toscano Tumori, Italy*
[b] *Translational Research Unit, Hospital of Prato, Istituto Toscano Tumori, Italy*

Triple-negative breast tumours are defined as oestrogen receptor (ER)-negative, progesterone receptor (PgR)-negative and human epidermal growth factor receptor 2 (HER2)-negative. Beyond this common negative triplet, however, triple-negative breast cancers (TNBC) are not an homogeneous subgroup. There is substantial intra-subgroup diversity in tumour biology, prognosis and treatment sensitivity.

Triple-negative breast cancer accounts for 15–20% of all breast cancer cases; however, it accounts for a disproportionate number of breast cancer relapses and deaths. Studies in early breast cancer have shown patients with TNBC to have a worse outcome compared with patients with non-TNBC [1]. Interestingly, neo-adjuvant studies highlight a subgroup of TNBC patients, approximately 20%, with highly chemosensitive disease and post-chemotherapy outcomes as favourable as their non-TNBC counterparts [2].

A key issue with TNBC is the accurate diagnosis of histological subtype and ER, PgR and HER2 status. ER, PgR and HER2 measurement has been associated with concerns regarding reliability and reproducibility, with remarkable reported rates of discordance. Furthermore, prior arbitrary thresholds for defining positivity for ER and PgR status, including 1%, 10% and 20%, have varied between laboratories and clinical trials. Clarity is offered by recent St Gallen and ASCO-CAP guidelines that define endocrine responsiveness as $\geqslant$1%. TNBC includes several morphological subtypes. Most are high-grade ductal carcinomas (not otherwise specified) but the triple-negative phenotype also occurs in medullary, apocrine and squamous cell carcinomas. Some subtypes, such as medullary carcinoma, are associated with a better prognosis and may not require aggressive chemotherapy.

In contrast to endocrine-sensitive and HER2-positive breast cancers, which are defined by the presence of specific targets for matched targeted therapy, there is currently no targeted therapy for TNBC. There are promising new targeted biological therapies, such as PARP inhibitors; however, chemotherapy remains the mainstay of systemic therapy for TNBC. The biological diversity displayed within TNBC does not support such an empirical approach; however, a lack of robust predictive biomarkers prevents a more individualised approach to the choice of adjuvant therapy.

Predictive markers could guide chemotherapy use by identification of the subset of TNBC patients with chemosensitive disease, or more specifically to predict sensitivity or resistance to individual chemotherapeutic agents. However, currently there are no clinical tools to recommend use, or omission, of specific chemotherapeutics. Conventional third-generation combination chemotherapy is the standard treatment. Rates of pathological complete response to conventional neoadjuvant anthracycline/taxane-based chemotherapy are reported to be within the range of 13–45% [2].

Optimal adjuvant systemic therapy for TNBC is difficult to define because of a lack of robust prospective data in triple-negative restricted trial populations. Most clinical data derive from retrospective exploratory subgroup analyses from biologically unselected trial populations, and small underpowered studies. Most data reveal a highly chemosensitive TNBC subset. Lack of randomised phase III trials with a standard therapy control arm make it difficult to determine whether this increased sensitivity is agent-specific or whether it reflects general sensitivity to chemotherapy (Fig. 1).

Triple-negative breast cancers are associated with a high proliferative rate, which may render them particularly sensitive to chemotherapy. Furthermore, a subset of TNBCs displays phenotypic overlap with *BRCA1*-mutation-related breast cancers. *BRCA1* is critical in homologous recombination, a cellular process of double-strand DNA damage repair, and in the cell cycle arrest necessary for DNA repair.

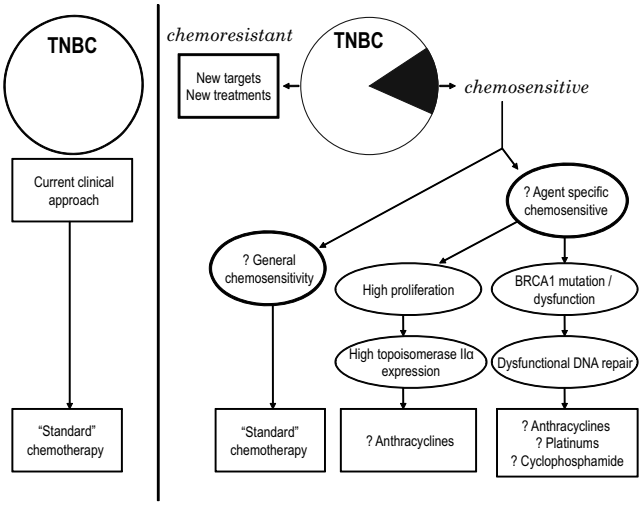

Fig. 1. Overview.

Loss of *BRCA1*, owing to a genetic mutation or post-genomic inactivation, may confer susceptibility to DNA-damaging agents, such as anthracyclines and platinums. Owing to the overlap between TNBC and *BRCA1*-mutation-associated tumours, it is tempting to extrapolate promising results for therapies in *BRCA1*-mutation-associated tumours to the larger subset of sporadic triple-negative tumours.

Regarding anthracyclines, pre-clinical and clinical data in TNBC are both limited and conflicting. Despite some results from meta-analyses and unpublished studies suggesting that additional benefit of anthracyclines over non-anthracycline-based therapy is restricted to HER2-positive disease, there is no conclusive evidence to date for omission of anthracyclines in TNBC. In the overall HER2-negative population, differential chemosensitivity in the TNBC subset will likely be lost in the majority of chemoresistant patients with an endocrine response. A recent meta-analysis of five trials compared anthracycline-based therapy versus CMF in four biological subgroups, defined using grade, ER, PgR and HER2 [3]. This exploratory analysis revealed significant superiority of anthracyclines in the HER2-positive cohort and also a trend for benefit in the moderately endocrine sensitive cohort and TNBC. In contrast, an exploratory analysis of anthracycline- vs. non anthracycline-based therapy, in which TNBC was further divided into core basal and non-basal disease based on CK5/6 and EGFR expression, revealed the superiority of the non-anthracycline-based therapy in the core basal subgroup [4]. Trials to define the role of anthracyclines specifically in TNBC patients are needed.

Renewed interest in platinums in breast cancer has been sparked by the overlap between TNBC and *BRCA1*-mutated tumours. Pre-clinical data reveal an association between *BRCA1* loss and platinum sensitivity; however, clinical data for carboplatin and cisplatin in TNBC are limited. Available data derive from small studies, retrospective analyses and *BRCA1*-mutated cohorts. Two small trials of single-agent neoadjuvant cisplatin report pCR rates of 72% and 15% in women with *BRCA1*-mutation-associated breast cancer and sporadic TNBC respectively [5,6]. It remains to be seen whether platinums are more effective than conventional chemotherapy in early TNBC, and indeed if heightened sensitivity of *BRCA1*-mutation-associated breast cancers extends to sporadic *BRCA1*-wild type TNBC.

With the current data, conventional anthracycline/taxane-based polychemotherapy remains the standard of care for patients with TNBC and non-TNBC. Promising results suggest sensitivity to DNA-damaging agents, but further data are required. For TNBC patients not cured by chemotherapy, identification of targetable tumour-addicted pathways is a clinical priority.

Conflict of interest statement

The authors have no conflicts of interest to disclose.

References

1 Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. *J Clin Onc* 2006;**24**:5652–7.

2 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.

3 Di Leo A, Desmedt C, Bartlett JM, et al. Final results of a meta-analysis testing HER2 and topoisomerase IIα genes as predictors of incremental benefit from anthracyclines in breast cancer. *J Clin Oncol* 2010;**28**:15s (abstract 519).
4 Cheang M, Chia SK, Tu D, et al. Anthracyclines in basal breast cancer: The NCIC-CTG trial MA5 comparing adjuvant CMF to CEF. *J Clin Oncol* 2009;**27**:15s (abstract 519).
5 Gronwald J, Byrski T, Huzarski T, et al. Neoadjuvant therapy with cisplatin in BRCA1-positive breast cancer patients. *J Clin Oncol* 2009;**27**:15s (abstract 502).
6 Silver DP, Richardson AL, Eklund AC, et al. Efficacy of neoadjuvant cisplatin in triple-negative breast cancer. *J Clin Oncol* 2010;**28**:1145–53.