Adjuvant systemic treatment for individual patients with triple negative breast cancer

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- Triple negative breast cancer
- Adjuvant chemotherapy
- Anthracycline
- Platinum

Chemotherapy is the only evidence based adjuvant systemic treatment option in triple negative breast cancer (TNBC). Despite emerging results for targeted biological therapies for this subpopulation, lack of robust results does not currently support their use beyond the confines of a clinical trial. Conventional systemic chemotherapy remains the standard of care and is curative in a minority of patients. There is no defined standard chemotherapy and there is currently no robust, prospective, randomized data to advise different use of specific chemotherapy agents in TNBC as compared to non-TNBC. Data suggest high sensitivity to chemotherapy, however it is yet to be determined whether this increased sensitivity is agent/regimen specific or whether it reflects general chemosensitivity. This review will focus on systemic chemotherapy in early TNBC, particularly anthracyclines and platinums, and potential predictive tools to guide chemotherapy use.

Introduction

Triple negative breast cancer (TNBC) is a collective term for breast cancers which do not express the hormonal estrogen and progesterone receptors, and do not have amplification or overexpression of HER2. In contrast to endocrine sensitive and HER2 positive breast cancers which are defined by recognition of particular targets for matched targeted therapy, the TNBC cohort is defined by a collective lack of these targets. However within triple negative disease there appears to considerable diversity in biology, prognosis and treatment sensitivity.

In the absence of targeted therapy, conventional chemotherapy is the mainstay of systemic therapy for TNBC. Given the biological diversity within the triple negative subgroup, such a standard approach to adjuvant systemic therapy in TNBC may be inappropriate. However, tools for identification of the subset of TNBC patients with chemosensitive disease and predictive biomarkers to individualise use of specific chemotherapeutics remain elusive.

Triple negative breast cancer

Patients with TNBC account for approximately 15% of early breast cancer cases. TNBC occurs more frequently in younger women and is often aggressive, associated with a high rate of visceral and central nervous system relapse and death within 3 years of primary diagnosis. As a subgroup, TNBC has a poor prognosis compared with other breast cancer subgroups however the majority of patients are cured by multidisciplinary treatment for primary localised disease with 5 year disease free survival of approximately 70–80%. Some individuals with TNBC have an excellent outcome in the absence of adjuvant systemic intervention. Some patients display intrinsic resistance to chemotherapy and a minority of patients will be cured by (neo)-adjuvant chemotherapy. Indeed in a minority of TNBC patients chemotherapy appears much more effective than in non-TNBC disease. The patients not curable by current therapy represent a cohort in urgent need of novel therapeutic approaches.

TNBC is an immunohistochemical diagnosis which 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 individuals, such as those with the medullary subtype, may have a better prognosis and may not require aggressive chemotherapy. Medullary breast cancer is rare, accounting for less than 1% of invasive breast cancer. Its relatively favorable prognosis was evident in a retrospective comparison of central pathology laboratory confirmed ER negative, high grade medullary cancers (n = 47) and ductal infiltrating cancers (n = 1407). Patients with medullary tumors had less vascular invasion, better disease free survival and better overall survival compared with the ductal subtype. Morphological subtype merits consideration in decisions regarding adjuvant therapy.

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There is substantial but incomplete overlap between immuno-
histochemistry defined TNBC, molecularly defined basal-like breast
cancer and BRCA1 mutation associated breast cancer. Approxi-
mately 80% of TNBC have a basal-like molecular profile.4 Beyond
the basal-like profile, TNBC encompasses other molecular intrinsic
subtypes, particularly normal-like and the recently described
claudin-low. As overlap between TNBC, basal-like breast cancer
and BRCA1 mutation associated breast cancer is incomplete, these terms
cannot be used synonymously.

Chemotherapy

Despite the promise of new targeted biological therapies, chemotherap-
ny remains the mainstay of systemic therapy for TNBC. There is no current robust
evidence to recommend use, or omission, of specific chemotherapy agents in the TNBC subset. Conventional
third generation combination chemotherapy is the standard clinical
strategy exploiting defective DNA repair in BRCA-associated
tumours, it is tempting to extend promising therapeutic
effects to other breast cancer subtypes.5

Due to the phenotypic similarities between TNBC and BRCA1
associated tumours, it is tempting to extend promising therapeutic
effects to other breast cancer subtypes.5

Table 1

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>No. of TNBC pts</th>
<th>pCR %</th>
<th>Reference</th>
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<tbody>
<tr>
<td>TNBC (immunohistochemical diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEC</td>
<td>40</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>AT</td>
<td>47</td>
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<td>9</td>
</tr>
<tr>
<td>FEC/FAC</td>
<td>120</td>
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<tr>
<td>Anthracycline-based therapy and/or taxane</td>
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<tr>
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<tr>
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<td>13</td>
</tr>
<tr>
<td>TAC/TAC → XN</td>
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<tr>
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<tr>
<td>AC/AT+paclitaxel + capecitabine</td>
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<td>34</td>
<td>15</td>
</tr>
<tr>
<td>AC → paclitaxel</td>
<td>45</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>AC → docetaxel or AC → paclitaxel or Paclitaxel → FAC</td>
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<td>43</td>
<td>17</td>
</tr>
<tr>
<td>Paclitaxel → FAC</td>
<td>22</td>
<td>45</td>
<td>18</td>
</tr>
<tr>
<td>AC: doxorubicin, cyclophosphamide; AT: doxorubicin/docetaxel; FAC: fluorouracil/doxorubicin/cyclophosphamide;</td>
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<td></td>
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</tr>
<tr>
<td>FEC: fluorouracil/epirubicin/cyclophosphamide; pCR: pathological complete response; TAC: docetaxel/doxorubicin/</td>
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<tr>
<td>cyanoplatin. XN: capecitabine/vinorelbine.</td>
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Early TNBC is associated with a paradox: a minority of patients
have highly chemosensitive disease but the subgroup as a whole
has poor disease free and overall survival. This was highlighted by
a neoadjuvant analysis in which TNBC patients attaining pCR had an
excellent outlook (3 year overall survival 94% vs 98% for non TNBC) 
whereas TNBC patients not attaining a pCR had a high likelihood of
systemic relapse (63% vs 76%, respectively) and death (74% vs 89%,
respectively) within 3 years of primary diagnosis.1

Several limitations are recognised in the quest for determin-
ination of optimal adjuvant chemotherapy for TNBC. There is
a lack of robust prospective data in triple negative restricted
trial populations. Most clinical data derives from retrospective
exploratory subgroup analyses and underpowered studies. Most results suggest high sensitivity to chemotherapy in TNBC. However
due to lack of randomised phase trials with a conventional control
arm, it is yet to be determined whether this increased sensitivity is
agent specific or whether it reflects general chemosensitivity.

Some analyses have explored differential chemotherapy benefit
in retrospectively defined biological subgroups. Studies which
bisect the biologically unselected trial population using an isolated
parameter, such as ER19 or HER2,20 are difficult to translate to
individuals as the the biological heterogeneity within the groups
is substantial. In such analyses, TNBC patients will be classified
as ER negative (a cluster of TNBC and HER2 positive disease) or
HER2 negative (a cluster of endocrine responsive disease and TNBC).
Such analyses, by their design, presume equal chemosensitivity
within all ER negative or all HER2 negative tumours. Differential
chemosensitivity in a minority subset of the minority TNBC cohort
will likely be lost.

More recently, exploratory retrospective analyses have been
undertaken in biological subgroups defined by clinical immuno-
histochemical profiles and research based molecular profiling.21-24
These are detailed below. Such profiles have prognostic value, but
a predictive role is yet to be robustly demonstrated.

From a biological viewpoint one may hypothesise preferential
chemotherapy benefit in TNBC due to its high proliferative rate
and overlap with BRCA1 mutation related breast cancers. BRCA1
is critical in homologous recombination, a cellular process of
double strand DNA break repair, and in the cell cycle arrest
necessary for DNA damage repair. Loss or inactivation of BRCA1
may impart particular susceptibility to DNA damaging agents, such
as anthracyclines and platinum. Furthermore, anthracyclines may
be active in TNBC due to proliferation driven upregulated expression
of the anthracycline drug target topoisomerase II alpha (topoIIα).

Due to the phenotypic similarities between TNBC and BRCA1
associated tumours, it is tempting to extend promising therapeutic
strategies exploiting defective DNA repair in BRCA-associated
tumors to the larger subset of sporadic TN tumors. Caution must
be heeded. Much as the terms TNBC, basal-like breast cancer and
BRCA1 associated breast cancer cannot be used synonymously due
to incomplete overlap, extrapolation of treatment results between
these groups is inappropriate. Extrapolating BRCA1 findings to the
entire triple negative cohort would be assuming loss or dysfunction of BRCA1 across the cohort. Biological heterogeneity within the TNBC cohort prevents such an assumption.

**Anthracyclines in triple negative breast cancer**

Anthracyclines, specifically doxorubicin and epirubicin, are among the most active agents for breast cancer. In biologically unselected early breast cancer populations, anthracycline containing therapy imparts an overall survival benefit. In one study, blockade of the topoII enzyme prior to exposure to the topoII inhibitor markedly reduced cytotoxicity and eliminated any differential BRCA effect, highlighting indirect DNA damage via binding of the cytotoxic to topoII protein rather than direct DNA damage. Conversely, other invitro work shows greater sensitivity to doxorubicin in BRCA1 wild type than in BRCA1 mutant breast cancer cells.

In the neoadjuvant setting, a retrospective analysis of 55 patients with TNBC treated with fluorouracil, epirubicin and cyclophosphamide (PEC), of whom 12 had a BRCA1 mutation, demonstrated an overall pCR rate of 42% (23/55). Notably only 2 of the 12 patients with BRCA1 mutation (17%) had a pCR. In contrast, 2 independent studies report high sensitivity of germline BRCA1 mutated tumours to anthracycline with pCR rates of 53% and 44%, respectively. In a sea of inconsistent and underpowered data from individual retrospective analyses of adjuvant trials, two recent meta-analyses suggest that anthracycline benefit in breast cancer is restricted to HER2 amplified disease. HER2 positive status defined a population more sensitive to anthracyclines than cyclophosphamide, methotrexate and fluorouracil (CMF), however the notion of equivalent anthracycline resistance in all HER2 negative disease is weakened by biological heterogeneity within the HER2 negative group. The majority of HER2 negative tumors are endocrine-responsive relatively chemoresistant, luminal A patients. Efficacy in the triple negative minority will be confounded by the chemoresistant major.

A recent meta-analysis of 5 trials compared anthracycline-based therapy versus CMF in 4 biological subgroups, defined using grade, ER, PgR and HER2. This exploratory, event-free survival analysis revealed statistically significant superiority of anthracyclines in the HER2 positive cohort (n = 153; Hazard ratio (HR) 0.70 (95% confidence interval (CI) 0.51–0.96)). However, benefit did not appear to be confined to HER2 positive disease as a trend for anthracycline benefit also extended to the moderately endocrine sensitive cohort (n = 378; HR 0.84 (95%CI 0.69–1.03)) and TNBC (n = 231; HR 0.82 (95%CI 0.63–1.07)). A limitation of this meta-analysis is that the TNBC was not further explored by basal-like and non basal-like subgroups.

In an exploratory subgroup overall survival analysis of the Canadian NC1-MA5 trial, contrasting results were reported. This trial compared cyclophosphamide, epirubicin and 5-fluorouracil (CEF) to CMF in node positive premenopausal women, and did further subgroup TNBC as core basal (n = 70) and non-basal (n = 29) based on the expression of basal markers CK5/6 or EGFR. Inferior efficacy from CEF compared to CMF was reported in the core basal subtype (5 year overall survival 51% vs 71%, respectively). In non-basal TNBC, no significant difference was seen however numbers are too small to draw conclusions (CEF n = 9, CMF n = 20).

Thus, available data are interesting but conflicting. No current prospective trial is addressing the question of anthracycline efficacy in the triple negative subgroup. The US Oncology Trials Group trial NCT00493870 is assessing anthracycline omission in patients with HER2-negative disease, namely docetaxel and cyclophosphamide (TC) versus docetaxel, Adriamycin and cyclophosphamide (TAC). However, within HER2-negative disease, any differential benefit in the TNBC minority will likely be confounded by the relative cheomesistance and favorable prognosis of the ER positive, HER2 negative luminal breast cancer majority. Trials to define the role of anthracyclines specifically in TNBC patients are needed. With available evidence, anthracyclines should still be considered an important component of chemotherapy for TNBC.

**Platinums in triple negative breast cancer**

In years past, platinums were explored in biologically unselected breast cancer populations as single agents and in combination therapy. They showed relatively high toxicity and no particular benefit over less toxic options. Renewed interest in platinums as DNA damaging agents has been sparked by the overlap between TNBC and DNA repair dysfunctional BRCA mutated tumors, and better management of acute toxicity.

Breast cancer cell lines and murine models lacking functional BRCA1 have shown high sensitivity to platinums. In TNBC cell lines, a novel mechanism for cisplatin sensitivity was highlighted in a molecular pathway study in which co-expression of p63/p73, which occurs in up to one third of TNBC, was associated with marked platinum sensitivity.

Clinical data for carboplatin and cisplatin in TNBC is limited, with data predominantly emerging from small studies and retrospective analyses. In the neoadjuvant setting, marked sensitivity to cisplatin has been reported in BRCA1 mutated breast cancer. In a small study, 9 of 10 women (90%) with TNBC and a BRCA1 mutation had a pCR with single agent cisplatin. The same study was extended to a total of 25 women with a BRCA1 mutation associated early breast cancer regardless of intrinsic molecular subgroup, with pCR documented in 18 patients (72%). In a related report by the same group, 102 women with a BRCA1 mutation who had received neoadjuvant chemotherapy, including the cisplatin patients from the 2 prior reports, were retrospectively identified. The pCR rate overall was 24%, however rates varied substantially per treatment: the pCR for cisplatin alone was 83%, compared with 7% for CMF, 8% for doxorubicin and docetaxel and 22% for anthracycline-based treatment.

In TNBC a small neoadjuvant study tested 4 cycles of single agent cisplatin in 28 patients, 2 of whom had a germline BRCA1 mutation. The pCR rate was 22%. Both patients with germline BRCA1 mutation had pCR. In the patients with sporadic TNBC, 4 of 26 patients had a pCR (15%). BRCA1 mRNA expression was variable but did not correlate with pCR. This study is small and lacks a control arm, but it highlights activity of single agent cisplatin in unselected TNBC, albeit at lower activity than reported in BRCA1 mutation cohorts and lower activity than reported with conventional neoadjuvant polychemotherapy regimens. Other neoadjuvant studies have assessed platinums in combination therapy in TNBC and report high activity. See Table 2.

The only randomised phase II data testing the incorporation of cisplatin in TNBC comes from the metastatic setting. A single institution trial in 126 TNBC patients pretreated were randomised to metronomic oral cyclophosphamide and methotrexate with or without cisplatin as second line therapy, following prior anthracycline and taxane therapy. Results favored incorporation of cisplatin, with improvement in overall response rate from 33 to 63%, median time to progression from 7 to 13 months, and median overall survival from 12 to 16 months.
Other studies in the metastatic setting report promising activity in TNBC with platinum combination therapy, notably in doublet therapy in the first line with gemcitabine, and in pre-treated metastatic patients with irinotecan, paclitaxel and cetuximab.

Despite promising results, it remains to be seen whether platinums are more effective than conventional chemotherapy in early TNBC. The issue of cross-sensitivity between carboplatin and cisplatin is also to defined. As such there is currently no evidence to support adjuvant platinum use outside a clinical trial. Trials in the neoadjuvant and metastatic settings may clarify the place for platinums in TNBC. NCT00861705/CALGB 40603 in TNBC is a 2×2 factorial design with a control arm of neoadjuvant paclitaxel followed by doxorubicin/cyclophosphamide (AC) evaluating the effect of addition of carboplatin and/or bevacizumab. NCT00432172/GEICAM/2006–03 in HER2 negative disease is comparing neoadjuvant epirubicin and cyclophosphamide followed by either cisplatin or taxane. NCT00589238 in TNBC is testing neoadjuvant paclitaxel with or without carboplatin, followed by AC. In the metastatic setting, NCT00532727/TNT in TNBC is comparing first line treatment with carboplatin or docetaxel.

**Neoadjuvant platinum based therapy in TNBC**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of TNBC pts</th>
<th>TNBC pCR (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>28</td>
<td>22</td>
<td>40</td>
</tr>
<tr>
<td>Cisplatin+paclitaxel</td>
<td>30</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>Carboplatin + paclitaxel</td>
<td>12</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>ECF</td>
<td>74</td>
<td>62</td>
<td>45</td>
</tr>
<tr>
<td>ECF</td>
<td>28</td>
<td>88</td>
<td>46</td>
</tr>
</tbody>
</table>

**Taxanes in triple negative breast cancer**

In early breast cancer trials, in populations unselected for biology, the addition of taxanes to adjuvant anthracycline based therapy has been tested in in several clinical trials. Most trials and a recent meta-analysis reveal additional benefit from taxane for disease free and overall survival. Results specifically in TNBC are limited, however preferential benefit of microtubule stabilising agents has not been demonstrated.

Potential biological bases for taxane sensitivity in TNBC are the high tumor proliferative rate and the presence of aberrant p53 in about 50% TNBC. Proposed p53 independent taxane cytotoxicity has not been supported by prospective clinical data. In pre-clinical studies, BRCA1 deficient breast cancer cell lines which showed increased sensitivity to topol alpha inhibitors and cisplatin showed decreased sensitivity to paclitaxel and vinorelbine.

The absolute benefit of taxanes when seen is modest and seems to be restricted to a minority of patients. Retrospective studies have explored the pivotal taxane trials to define sensitive subgroups. In CALGB 9344, the incorporation of sequential paclitaxel following AC was superior to AC alone in the ER negative, HER2 negative subgroup (HR 0.89 (0.79–0.99, p=0.027)). Similarly, in the PACS 01 trial comparing FEC with FEC followed by docetaxel, there was a significantly better metastasis-free survival and overall survival for the incorporation of docetaxel among patients with a basal-like profile, as defined by an immunohistochemical panel. Non significant trends in favor of taxanes in TNBC were seen in GEICAM 9805 which compared docetaxel, doxorubicin and cyclophosphamide (TAC) with fluorouracil, doxorubicin and cyclophosphamide (FAC) in node-negative high risk breast cancer, BCRG 001 TAC with FAC in node positive disease, and BIG 02–98 which compared assessed incorporation of sequential or concurrent docetaxel to an anthracycline/CMF control.

An additional benefit from a taxane has not been consistently observed in the triple negative subgroup. The TACT trial compared FEC followed by docetaxel to a control of FEC or FEC/CMF, with no significant difference between the treatment arms in TNBC. In PACS 04 which compared FEC100 with concurrent epirubicin and docetaxel, no differential effect was evident in TNBC.

**Alkylating agents in triple negative breast cancer**

Activity of alkylating agents in TNBC is challenging to ascertain. Cyclophosphamide is the most commonly used alkylating agent in breast cancer. Due to standard co-administration with an anthracycline and diversity in scheduling (intermittent versus metronomic) there is limited data to specifically ascertain the role of cyclophosphamide. Retrospective studies suggest that TNBC may have particular sensitivity to alkylating agents.

Cyclophosphamide in low continuous dosing has been shown to exert an anti-tumor effect in breast cancer, attributed to a predominant anti-angiogenic effect. Specifically in TNBC, anti-angiogenic therapy is promising due to high reported VEGF levels. In the neoadjuvant SWOG 0012 study patients were randomised to neoadjuvant standard AC or metronomic AC. Metronomic chemotherapy appeared superior overall (pCR 27 vs 17%) and in the ER-PgR− subset (pCR 43 vs 26%). In the randomized Phase II trial in metastatic TNBC previously described comparing metronomic cyclophosphamide and methotrexate with or without cisplatin, the overall response rate in the control arm was 33%, while of 300 patients treated with neoadjuvant CMF, triple negative tumors presented the highest response rate as assessed by mammography. Response rate in TNBC was 64.9% compared with 51% for HER2 disease and 40% for luminal tumours. In node negative patients, classical CMF had differential effect across IHC subgroups, with the greatest benefit in TNBC.

**Predictive tools for chemotherapy response**

Tools to individualise chemotherapy use in TNBC are missing. To date, biomarker studies for chemotherapy benefit have been disappointing. Emergence of robust, prospectively validated predictive biomarkers may identify patients with sensitive, or just as importantly insensitive, disease.

Immunohistochemical and molecular profiling platforms have enabled classification of breast cancer subgroups with similar features. However, recognition of further diversity in biology and treatment sensitivity within the subgroups requires new approaches which classify based on targetable events. These may be class specific but they may also be independent of molecular subclass. Optimal chemotherapy use may be achieved by matching chemotherapeutic mechanisms of action with a high likelihood of response based on demonstrable vulnerability to therapy. This vulnerability may be identified may be increased functional biological targets, such as high topol expression for anthracyclines, or assessment of cell pathway function, such as DNA repair capacity for DNA damaging chemotherapy. Other features with emerging importance in response to chemotherapy, beyond the scope of this review, include intra-tumoral biological heterogeneity and influential host features, particularly the host stroma and immune defenses contained in the peri-tumor microenvironment.

**Topoisomerase II alpha**

A predominant mechanism of action of anthracyclines is DNA damage via binding to the topol protein, an enzyme which
relieves torsional stresses created by separation of the supercoiled DNA double-helix during transcription and replication. Inhibition of topolα leads to double-strand DNA breaks, with cell death if DNA damage repair mechanisms are inadequate. Many studies have assessed topolα at the level of gene, mRNA and protein yielding inconsistent results.31,64–67

Tumors may overexpress topolα without TOP2A amplification, attributable to multifactorial regulation of transcription and translation. One of the most potent promoters of topolα expression is cell proliferation. In TNBC, TOP2A is seldom if at all amplified, however the high proliferative rate frequently results in high topolα expression. This was highlighted in an analysis of 31 TNBC patients, in whom none had TOP2A amplification however 80% had high topolα expression.68 The topolα protein, not the gene, is the anthracycline target. Thus correlation between anthracycline and drug target should be downstream at the protein level. Regarding the protein, variable mRNA splicing creates protein isoforms with implications for function and intracellular localisation.69 The active site of the protein, variable mRNA splicing creates protein isoforms with implications for function and intracellular localisation.69 The active

DNA damage

Several studies have explored potential markers of DNA damage and prediction of sensitivity to DNA damaging therapy. One such tool is the comet assay. Comet allows rapid detection and quantification of DNA strand breaks in individual cells.71 In this assay, fluorescence-tagged damaged DNA fragments from single gel-embedded cells migrate differentially during electrophoresis. Using fluorescence microscopy, cells with DNA damage appear as ‘comets’ due to tails of DNA fragmentation. The extent of damage is reflected in the comet tail length and comet tail intensity. The standard comet assay is able to provide information about DNA damage, while modified applications of comet also provide more specific data for types of DNA damage and intrinsic DNA repair capacity to an external insult.71,72 Comet has been applied to demonstrate innate DNA damage in breast cancer cells, with substantial variation between and within intrinsic molecular subgroups.73

DNA repair proteins may demonstrate cellular vulnerability of DNA damaging agents. A neoadjuvant study used immunofluorescence microscopy to assess the damage repair protein Rad51 on a biopsy taken 24 hours after doxorubicin or epirubicin based chemotherapy for sporadic primary breast cancer.74 Rad51 foci form in response to DNA damage at sites of damage. Low Rad51 foci formation correlated with higher pCR. Another neoadjuvant study assessed a panel of DNA repair proteins involved in homologous recombination on primary breast tumour biopsies at baseline and 18–24 hours after epirubicin/cyclophosphamide chemotherapy.75 The panel of DNA repair proteins assessed by immunohistochemistry included BRCA1, Rad 51, γH2AX, and conjugated ubiquitin (at baseline) and Rad 51 (post treatment). DNA damage response score was assessed from 0 to 4, with the highest score reflecting the greatest efficacy in DNA repair. The DNA response score showed an inverse correlation with tumour shrinkage and response rate. At a molecular level, a promising study reported a multigene DNA repair signature, derived from patients with BRCA-1 mutation associated tumors, which identified sporadic TNBC with ‘BRCaness’ and anthracycline sensitivity.76 These results are promising, but still preliminary.

Conclusion

As a subgroup, TNBC is aggressive. Within the subgroup, biological diversity is recognized but must be further explored. In a subgroup of individuals with TNBC adjuvant systemic therapy is not required due to an excellent prognosis. In a subgroup, conventional polychemotherapy is curative. Promising preliminary results suggest particular sensitivity to DNA damaging chemotherapeutics due to mutant or dysfunction BRCA with resultant impairment in homologous recombination. Optimal choice and scheduling of chemotherapy is yet to be defined. The use of chemotherapeutic agents in a targeted manner may be guided by predictive tools, which may be identified by well designed, prospective, biologically driven trials in TNBC. Mandatory tissue collection in such trials enriches research potential. For patients not cured by chemotherapy, we strive to identify tumor addicted pathways which may be therapeutically targeted.

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Conflict of interest statement

A. Di Leo: Speakers Bureau: AstraZeneca, GSK, Pfizer, Roche, sanofi-aventis, Cephalon. C. Oakman, E. Moretti, F. Galardi, C. Biagioni, L. Santarpia and L. Biganzoli have no conflict of interest to declare.

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