The Triple-Negative Subtype: New Ideas for the Poorest Prognosis Breast Cancer

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Triple-negative breast cancer accounts for about 15%–20% of all breast cancers. Patients with triple-negative subtype have a significantly increased risk of relapse and death. A panel of specific molecular alterations like high rate of p53 mutations, frequent loss of function of BRCA1, and several tyrosine kinase activations has been shown in this specific phenotype. An optimal chemotherapy regimen for these cancers remains to be determined, representing a major challenge for patient management. DNA alkylating agents, as cisplatin, were shown to be particularly effective in the neoadjuvant setting for patients with the disease. Targeted therapies are being successfully developed. Poly (ADP-ribose) polymerase-1 inhibitors induce tumor response as a single agent in BRCA1-mutated breast cancer and might sensitize cancer cells to cisplatin in the triple-negative subpopulatation. Chemotherapy is a cornerstone of current clinical practice for this type of disease. Progress might derive from refined biology-driven phase II trials that will also integrate targeted agents with chemotherapy.


Triple-Negative Breast Cancer (TNBC)

TNBC, defined by the lack of immunohistochemical staining for estrogen receptors, progesterone receptors, and lack of overexpression or amplification of HER2/neu, has an aggressive biological behavior, marked by increased risk of recurrence and poorer survival compared with hormone receptor–positive subtypes (1–3). Several trials are currently focused on patients with TNBC. The clinical management of patients with early-stage or with metastatic TNBC will surely change in the forthcoming decade due to the general shift of treatment approaches based on molecular subtypes of the disease, focusing on genetic pathways which lead to accelerated proliferation of TNBC. Preclinical observations combined with evidence from clinical efficacy have focused attention on strategies targeting DNA repair defects and BRCA mutation–associated breast cancers (4). The natural history of TNBC is characterized by an increased risk of distant recurrence and death in the first 3–5 years after diagnosis followed by a rapidly declining risk of recurrence thereafter (5–7). Women with inherited mutations in one allele of the BRCA1 breast cancer susceptibility gene are at significantly elevated risk for developing invasive breast cancer (8). Intriguingly, when breast cancers develop in these women, it is of triple-negative phenotype in the majority of cases (9). The current standard of care for women with early-stage TNBC contains an anthracycline- and taxane-based combination chemotherapy regimen, although such “standard” is based on data from large adjuvant trials in women unselected for breast cancer subtype (10). A subgroup analysis of historical, pivotal adjuvant chemotherapy trials was conducted and has shown that women with hormone receptor–negative breast cancers derive the greatest incremental benefit from dose-dense doxorubicin and cyclophosphamide followed by paclitaxel compared with every 3-week dosing schedules (11,12). Several studies in the neoadjuvant setting have documented that the current standard combination chemotherapy, though of clear benefit in women with TNBC, is suboptimal, as evidenced by the poorer clinical outcomes of this group despite their greater chemosensitivity (5). The search for new therapeutic targets in TNBC is mandatory.

A Disease of DNA Repair

The excision repair pathways, including base excision repair, nucleotide excision repair, and mismatch repair, use a “cut and patch” mechanism to excise the damaged or incorrect DNA sequence and fill the resulting gap using the complementary DNA strand as a template (13). In addition to its role in homologous recombination, BRCA1 has been implicated as having roles in nucleotide excision repair and base excision repair. Poly (ADP-ribose) polymerase-1 (PARP1) is a member of a family of enzymes that synthesize poly(ADP-ribose) and has known functions in base excision repair. PARP1 is activated in response to DNA damage and catalyzes the formation of ADP-ribose polymers at sites of DNA damage (13). This relaxes the chromatin structure and facilitates recruitment of base excision repair proteins to the site of the DNA break. Over the past years, increasingly potent PARP inhibitors have been developed and evaluated for their potential role as general chemotherapy or radiation therapy sensitizers (13). BRCA1- and BRCA2-deficient cells were found to be markedly sensitive to inhibition of PARP, and this was in contrast to those cells wild type or heterozygous for BRCA1 or BRCA2 mutations (13). Inhibition of PARP with a small-molecule inhibitor in tumor cells genetically deficient in BRCA function mimics the situation of genetic loss of PARP and results in “chemical synthetic lethality” (13). At present, no PARP inhibitors are US Food and Drug Administration- or European Medicines Agency-approved for the treatment of patients with cancer, and data are lacking in an adjuvant patient population. A
number of pharmaceutical companies are developing PARP inhibitors for the treatment of patients with breast and other cancers. At least two compounds are in advanced development in breast cancer: iniparib (BSI-201; BiPar Sciences Inc [South San Francisco, CA]/Sanofi-Aventis U.S. [Bridgewater, NJ]) and olaparib (AZD-2281; AstraZeneca [Wilmington, DE]). Iniparib has been studied in a randomized phase II trial of gemcitabine and carboplatin with or without the PARP inhibitor. A total of 123 women with advanced TNBC treated with up to two previous chemotherapy regimens for metastatic disease were enrolled (14). This study demonstrated improvements in the clinical benefit rate (21% vs 62%; \(P = .0002\)), overall response rate (16% vs 48%; \(P = .002\)), median progression-free survival (3.3 vs 6.9 months; hazard ratio, 0.342; \(P < .0001\)), and median overall survival (5.7 vs 9.2 months; hazard ratio, 0.348; \(P = .0005\)) among patients who received iniparib in combination with chemotherapy. Tutt et al. (15) presented the results of a phase II study with the orally bioavailable PARP inhibitor olaparib for the treatment of women with BRCA1- and BRCA2 mutation–associated stage IIIB–IV breast cancer. The objective response rate was 41% in the higher-dose cohort (400 mg twice daily) and 22% in the lower-dose cohort (100 mg twice daily). A single-arm phase II neoadjuvant study of gemcitabine, carboplatin, and iniparib for women with stage I–III A (tumor diameter ≥ 1 cm) TNBC is ongoing. Pfizer, Inc, is exploring the efficacy of adjuvant cisplatin, with or without the PARP inhibitor PF-01367338, in a randomized phase II study in patients with early-stage, triple-negative, or BRCA mutation–associated breast cancer with residual disease after neoadjuvant chemotherapy. Understanding the determinants of response to these agents will be critical to accelerate the development of this targeted treatment in a curable patient population. The adjuvant setting will be important to carefully assess the risk of secondary malignancies and other long-term toxicities.

**Alkylating Agents and TNBC**

The family of platinum salts, now also including carboplatin and oxaliplatin, exerts its therapeutic efficacy through production of direct DNA damage. These agents bind to DNA directly and result in the formation of DNA-platinum adducts and, consequently, intrastrand and interstrand DNA cross-links that impede cell division. Currently, the role of platinum chemotherapy in the adjuvant treatment of patients with breast cancer is limited. In women with HER2-positive breast cancer, the combination regimen of docetaxel, carboplatin, and trastuzumab is now a standard alternative to an anthracycline-, taxane-, and trastuzumab-containing regimen (16). Recently, there has been renewed interest in investigating the role of platinum chemotherapy in the TNBC subtype based on the hypothesis of greater susceptibility of this breast cancer subtype to DNA damage. Clinical data in patients with early-stage TNBC are limited. A number of studies investigated the role of platinum chemotherapy in the neoadjuvant treatment of patients with early-stage TNBC (17–20). Table 1 summarizes all these trials. Because pathological complete response (pCR) is an important surrogate endpoint for breast cancer survival, the neoadjuvant strategy is particularly well suited to the evaluation of novel agents and combinations for these patients. The upcoming CALGB (Cancer and Leukemia Group B) randomized phase II neoadjuvant trial 40603 will examine the additive benefit of carboplatin when added to taxane chemotherapy following doxorubicin and cyclophosphamide (AC) regimen in women with stage II/III TNBC. The randomized design will provide important insight into the role of platinum chemotherapy in the treatment of patients with this disease. Importantly, the neoadjuvant approach allows assessment of a new regimen’s activity in a relatively small number of patients over a short time period; moreover, collection of tumor tissue before and after neoadjuvant treatment provides a unique opportunity for correlative translational science.

Recently, some reports have been published showing a benefit from the use of classical cyclophosphamide, mohotrexate, and fluorouracil (CMF) in patients with triple-negative tumors (21–23). As alkylating agent, also cyclophosphamide chemotherapy can also induce direct DNA damage in TNBC. Among these, a study by Colleoni et al. (23) highlights a larger magnitude of benefit of classical CMF in patients with triple-negative node-negative breast cancer after a median follow-up of 11 years. In this report, authors evaluated patterns of recurrence according to treatment received in a group of patients (n = 2257) enrolled in IBCSG (International Breast Cancer Study Group) trials VII–IX with node-negative breast cancer, randomized to receive classical CMF for three or six cycles with or without endocrine therapy vs endocrine therapy alone. Patients with triple-negative tumors were 303 (15%), and chemotherapy significantly improved 10-years disease-free survival in this subtype group (73% vs 57%, \(P = .007\)) (23).

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Regimen</th>
<th>pCR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver et al. (17)</td>
<td>28</td>
<td>Cisplatin monotherapy</td>
<td>21 (9 to 43)</td>
</tr>
<tr>
<td>Fraschi et al. (18)</td>
<td>74</td>
<td>Cisplatin/epirubicin/paclitaxel</td>
<td>62 (50 to 73)</td>
</tr>
<tr>
<td>Torrisi et al. (19)</td>
<td>30</td>
<td>Cisplatin/epirubicin/5-FU</td>
<td>40 (23 to 59)</td>
</tr>
<tr>
<td>Ryan et al. (20)</td>
<td>51</td>
<td>Cisplatin/bevacizumab</td>
<td>15</td>
</tr>
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* CI = confidence interval; pCR, pathological complete response; 5-FU, 5-fluorouracil.

**Targeting Angiogenesis in TNBC**

Several clinical trials are ongoing to evaluate the role of angiogenesis inhibitors in the treatment of patients with early-stage TNBC. Preliminary results from a single-arm phase II neoadjuvant study of cisplatin, in combination with bevacizumab before surgery in patients with early-stage TNBC, showed that a pCR was observed in 15% of 46 evaluable patients and an additional 22% of partial response (20). The randomized phase III neoadjuvant CALGB 40603 trial, which will evaluate the benefit of carboplatin added to AC followed by paclitaxel in a triple-negative patient population, will also examine the added benefit of bevacizumab in a 2 × 2 factorial design. The BEATRICE (Bevacizumab Adjuvant Therapy in Triple Negative Breast Cancer) study is an ongoing randomized phase III study that will examine the efficacy of standard chemotherapy, with or without bevacizumab, in an adjuvant triple-negative patient population. In a phase II trial that evaluated sunitinib single
agent, this drug was associated with a 15% response rate in patients with TNBC (24). Although the sample size was small, the observation of an objective response in a few patients once again suggests that the drug could have some effect in selected patients. A large randomized phase II trial completed accrual and compared activity of sunitinib as monotherapy with chemotherapy in 200 patients with TNBC.

Conclusions
A growing understanding of the molecular pathways of TNBC subtype will lead to the development of novel targeted strategies. TNBC shares many similarities with breast cancers arising in women with germline mutations in BRCA1. Oncogenic events can be shared across molecular classes of breast cancer. No first-in-class agent can be identified for TNBC, but clear sensitivity to DNA damaging agents in the neoadjuvant, adjuvant, and/or metastatic settings has been observed. Integrated biology approaches with improved molecular characterization and functional profiling of the DNA repair activity of these tumors will facilitate rational trial designs and improve patient selection for new targeted treatments.

References

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