

Recent Updates in the Management of Triple Negative Breast Cancer

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Abstract

Triple negative breast cancer is the most aggressive subtype of breast cancer, characterized by a lack of targeted therapy. Neoadjuvant chemotherapy is used to understand disease biology; patients who attain a complete pathologic response have improved outcomes compared to those who have residual disease. Locoregional treatment options remain similar to other types of breast cancer. Further research to identify druggable targets is ongoing and new agents appear to be on the horizon.

Keywords

Triple negative, radiation therapy, neoadjuvant chemotherapy

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Triple negative breast cancer (TNBC) is a subtype of breast cancer that comprises 15–20% of all breast cancer cases and is characterized by aggressive clinical features.¹ Compared to estrogen receptor (ER)-positive cancers, it carries an increased risk for relapse within five years of diagnosis, increased propensity for spread to viscera like lungs and brain, and a lower incidence for bony metastases. TNBC is more common in younger women (<50 years old), African Americans, and those with *BRCA1* germline mutations. Although only 10–20% of all TNBCs harbor *BRCA1* mutations, TNBC is the subtype seen in 75% of *BRCA1* carriers who develop cancer. Because TNBC is the dominant subtype in *BRCA1* carriers, genetic testing is recommended for all cases of TNBC in women younger than 60 years. The results, if positive, have implications in choices of local treatment, including a propensity to select ipsilateral and prophylactic contralateral mastectomies over a breast conserving treatment approach.

By definition, treatment options for these tumors do not include endocrine or human epidermal growth factor receptor 2 (HER2)-directed therapies, thus existing combinations of cytotoxic agents are the backbone of systemic treatment for TNBC. Delivering therapy in the neoadjuvant setting provides the added benefit of obtaining prognostic information, since patients without pathologic complete response (pCR) fare significantly worse than those with pCR. For example, TNBC with pCR is reported to achieve three-year overall survival (OS) of 94%, similar to survival outcomes of non-TNBC ($p=0.24$), compared to three-year overall survival (OS) of 68% for patients with residual disease, which is significantly worse than non-TNBC subtypes ($p<0.0001$).¹ Identifying those who benefit from neoadjuvant therapy is important not only for optimization of regimens that result in a pCR, but to further identify or

elucidate common characteristics of subgroups who do not respond and develop novel approaches to this subgroup.

The recent reports at the 2015 San Antonio Breast Cancer Symposium (SABCS) lend some insight into translating pCR into survival outcomes. The German GeoparSixto study reported improved disease free survival (DFS) in TNBC patients receiving neoadjuvant platinum-based chemotherapy compared to standard chemotherapy alone.² Of TNBC patients treated with carboplatin, 35-month DFS was 85.8% compared to 76.1% in the control arm (hazard ratio [HR] 0.56 $p=0.035$). Though results came from a subset analysis of the TNBC subtype population, the findings are concordant with initial findings of improved pCR rates with platinum-based chemotherapy. The authors concluded the results support the use of platinum agents in neoadjuvant regimens for TNBC. Though additional subset analysis of TNBC patients with and without *BRCA* germline mutations suggested that DFS benefit was higher in those with wild-type *BRCA* status, these data should be considered hypothesis generating as the number of women with *BRCA* mutations was small ($n=50$) and this finding conflicts with previous studies that found platinum compounds were not active in *BRCA* wild-type patients.

Similarly, the CALGB 40603 study reported statistically significant higher rates of pCR in TNBC who received neoadjuvant platinum-based chemotherapy.³ In contrast, however, the secondary endpoints of event-free survival (EFS) and OS presented at SABCS 2015 showed that the presence of pCR predicted improved EFS and OS, regardless of chemotherapy arm.⁴ The authors acknowledged the study was underpowered to detect a significant advantage when comparing carboplatin or bevacizumab with standard neoadjuvant chemotherapy. Additional data are necessary before

neoadjuvant platinum-based therapy can be considered standard treatment for TNBC. Current investigations of the homologous recombination deficiency (HRD) assay, a marker of genomic instability, may allow for further prediction of patients who respond to platinum-based chemotherapy.⁵

In the setting of neoadjuvant chemotherapy, the approach to locoregional treatment is not modified based on response but instead is recommended based on pre-treatment characteristics such as tumor size and nodal involvement.⁶ Local treatment options include breast-conserving therapy (BCT), defined as breast conserving surgery followed by radiation therapy (RT), or alternatively, mastectomy, with or without post-mastectomy radiation therapy (PMRT). Though the concern for higher locoregional recurrence (LRR) may indicate the need for more aggressive locoregional treatment (i.e. mastectomy), patients with basal-like TNBC undergoing mastectomy also remain at higher risk for LRR.⁷ Hence, TNBC is not a contraindication for breast conservation therapy, because the increased LRR risks (relative to luminal subtypes) appear to be irrespective of whether the patient has mastectomy or breast conservation.⁸ Nevertheless, local-regional management of TNBC remains controversial, as present guidelines do not incorporate consideration of breast cancer subtypes in their recommendations. For example, it remains unclear whether the indications for PMRT in the TNBC setting should be different than with other subtypes. Recently, a large Netherlands tumor registry dataset analysis, reported at Society for Surgical Oncology's Annual Meeting 2016, suggesting that the risk for local recurrence of breast cancer as a first event decreases as event-free survival lengthens. This study reported that the decrease in local relapse risk with event-free interval was most pronounced for TNBC, with local relapse at 1, 2, and 3 event-free years being 4.6%, 2.7%, and 1.6%, respectively.⁹ Hence, isolated loco-regional recurrences are often overshadowed by the risks of distant disease in TNBC. Unfortunately, the development of guidelines specific to locoregional management of TNBC will not exist until additional data become available.

For TNBC patients undergoing BCT, the uniform adoption of the Society of Surgical Oncology/American Society for Radiation Oncology (SSO/ASTRO) negative margins definition of 'no ink on tumor' has been an area of controversy, with concerns that wider margin widths may be necessary for TNBC.¹⁰ A review of women with TNBC who underwent BCT between 1999 and 2009 analyzed local relapse as a function of margin status stratified into two groups (0.1–2.0 mm versus >2 mm widths), and reported no difference in LRR between the two margin width groups. This

findings further support the definition of negative margin as 'no tumor on ink' for TNBC.¹¹

Additional treatment options for TNBC will evolve as subtypes within this heterogeneous subgroup are identified, and novel and current treatment modalities are combined and further explored. For example, current investigations are assessing the use of concomitant cisplatin with radiation therapy in TNBC as a radiosensitizing agent; the use of additional adjuvant capecitabine after standard adjuvant chemotherapy for operable TNBC; zoledronic acid as adjuvant treatment, personalized polyepitope DNA vaccine strategies in TNBC with persistent disease following neoadjuvant chemotherapy, and combinations of standard neoadjuvant chemotherapies with poly ADP ribose polymerase (PARP) inhibitors. Furthermore, the use of gene expression profiles have identified molecular subtypes of TNBC cell lines may help align patients with specific therapies used to exploit their individual characteristics.¹² Women with metastatic TNBC with androgen receptor (AR) expression and an AR-related gene signature have been found to respond to enzalutamide, an AR-inhibitor used in castrate-resistant prostate cancer, suggesting a potential target for TNBC that is AR-positive.¹³ For the TNBC subgroup that express Trop-2 protein (a human trophoblast cell-surface antigen that is highly expressed in human carcinoma but rarely in normal tissues), a Trop-2 Antibody-Drug Conjugate (ADC) called sacituzumab govitecan (IMMU-132) has received Breakthrough Therapy Designation in 2016 by the US Food and Drug Administration, based on results presented at the American Association for Cancer Research (AACR) 2015 meeting that showed women with heavily pretreated metastatic TNBC had clinically meaningful disease control, defined as complete or partial response, or stable disease >6 months, of 46%, with limited toxicity.¹⁴ Initial estimates of Trop-2 protein are as high as 80%, suggesting a potentially promising targeted treatment for this population.

These are few of many examples of ongoing investigations to improve the outcomes for TNBC. The heterogeneity of TNBC demands a great need for novel therapeutic innovation. Different subtypes within TNBC might be sensitive to different therapeutic regimens based on their main underlying defects. The understanding and elucidation of the intricate differences in this population will allow more clarity for the development of targeted strategies attacking underlying vulnerabilities within each TNBC subtype, with the hopes of improving overall outcomes for all TNBC patients in the near future. ■

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