

Practical consensus recommendations on management of triple-negative metastatic breast cancer

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Abstract

Patients with breast cancer along with metastatic estrogen and progesterone receptor (ER/PR)- and human epidermal growth factor receptor 2 (HER2)-negative tumors are referred to as having metastatic triple-negative breast cancer (mTNBC) disease. Resistance to current standard therapies such as anthracyclines or taxanes limits the available options for previously treated patients with metastatic TNBC to a small number of non-cross-resistant regimens, and there is currently no preferred standard chemotherapy. Clinical experience suggests that many women with triple-negative metastatic breast cancer (MBC) relapse quickly. Expert oncologist discussed about new chemotherapeutic strategies and agents used in treatment of mTNBC and the expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at this practical consensus recommendations for the benefit of community oncologists.

Key words: AR testing, BRCA, germline mutation, poly (adenosine diphosphate-ribose) polymerase I inhibitors, programmed cell death ligand 1, rebiopsy

Introduction

With 246,660 new diagnoses and 40,450 deaths projected for 2016, breast cancer remains the most commonly diagnosed and the second leading cause of cancer-related deaths among women in USA.^[1] The prognosis of patients with metastatic breast cancer (mBC) is heterogeneous and can range from several months to many years depending upon many factors, including, but not limited to, estrogen and progesterone receptor (ER/PR) status and human epidermal growth factor receptor 2 (HER2) receptor status.^[2,3] Metastatic tumors that are ER/PR negative and HER2 negative are characterized as being triple negative and, although not considered synonymous, are generally thought to consist of tumors, which harbor a basal-like molecular subtype.

Most new treatment options for mBC recently approved by the Food and Drug Administration (FDA) are only effective for ER/PR-positive or HER2- positive metastatic tumors, and relatively few new agents have been approved for the subset of patients with metastatic triple-negative breast cancer (mTNBC). Single-agent chemotherapy continues to serve as the backbone of MBC treatment. The lack of efficacious therapy within this cohort, combined with the propensity to develop visceral or central nervous system (CNS) metastasis (as opposed to more indolent bone or soft tissue predominant metastases), has translated into an overall survival (OS) that has remained stagnant over the past 20 years.^[4-6] As a result, patients with mTNBC continue to have a considerably worse OS when compared to their mBC counterparts.

Expert group of oncologist meet in the update in oncology-X-2017 to discuss on available chemotherapeutic strategies and agents, including targeted therapy and

immunotherapy, in patients with metastatic triple-negative breast cancer (mTNBC).

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discuss about triple-negative breast cancer (mTNBC) in this chapter. While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.^[7,8] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr. Vedant Kabra whereas the discussions were moderated by Dr. B K Smruti and Dr. Ranga Rao. The core expert group consists Dr. Kishor Singh, Dr. Ajay Gupta, Dr. Sandeep Batra, Dr. R K Choudhary, Dr. Alok Gupta, Dr. Siddharth Sahai and Dr. Christopher Twelves. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use Fertility Prevention in Breast cancer patients.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.^[9-11] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their ersonal experiences, make

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comments and record dissent while voting for the consensus statements. Total of five broad question categories were part of the expert group discussions [Tables 1-6].

Metastatic triple-negative breast cancer — which is estrogen-receptor (ER)-negative and progesterone-receptor (PR)-negative and has no overexpression of human epidermal growth factor receptor type 2 (HER2) — is an aggressive subtype of breast cancer marked by higher rates of visceral and central nervous system metastases and poorer disease specific

Table 1: Question categories addressed by the update in oncology-X-2017

Broad question title
Question 1-40 years postmenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T2N0M0, triple negative. She takes adjuvant chemotherapy with Taxane based regimen and three years later develops lung and liver metastases. Good performance status and normal biochemistry
Question 1 (I) - What should be the next line of therapy?
Question 1 (II) - Will you ask for germline mutation testing?
Question 1 (III) - In BRCA1/2 positive cases, will you consider PARP inhibitors?
Question 1 (IV) - In such cases, do you regularly perform, AR testing?
Question 1 (V) - Have you started asking for PDL1 testing in these cases?
Update in oncology-X-2017

PARP=Poly (adenosine diphosphate-ribose) polymerase

Table 2: Question 1 (I) - What should be the next line of therapy?

Options (%)	Taxane based chemotherapy	Platinum and gemcitabine	Eribulin	Any other
Percentage of polled oncologists	75	0	25	0

Expert group consensus: Expert panel recommendation is re-biopsy for confirmation of unchanged biomarker status and then starting taxane single agent chemotherapy

Table 3: Question 1 (II) - Will you ask for germline mutation testing?

Options (%)	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Expert panel recommends germline mutation testing

Table 4: Question 1 (III) - In BRCA1/2 positive cases, will you consider poly (adenosine diphosphate-ribose) polymerase inhibitors?

Options (%)	Yes	No
Percentage of polled oncologists	75	25

Expert group consensus: Expert panel does not recommend PARP inhibitors in BRCA 1/2 positive relapsed triple negative breast cancer. PARP=Poly (adenosine diphosphate-ribose) polymerase

Table 5: Question 1 (IV) - In such cases, do you regularly perform, AR testing?

Options (%)	Yes	No
Percentage of polled oncologists	33.3	66.7

Expert group consensus: Expert panel does not recommend routine AR testing

Table 6: Question 1 (V) - Have you started asking for PDL1 testing in these cases?

Options (%)	Yes	No
Percentage of polled oncologists	57.1	42.9

Expert group consensus: Expert panel suggests testing for PDL1 at first relapse

survival than hormone receptor-positive subtypes.^[12-15] Patients with triple-negative breast cancer treated with preoperative chemotherapy have higher rates of pathological complete response than patients with hormone receptor-positive breast cancer.^[16,17] However, patients in whom metastatic disease develops have a very poor prognosis, with a median survival of approximately 1 year.^[18] No standard-of-care therapy exists for patients with metastatic triple-negative breast cancer, and therefore they have an unmet need.

Accounting for 15 to 20% of all cases of breast cancer,^[12,19,20] triple-negative breast cancer shares clinical and pathological features with hereditary *BRCA1*-related breast cancers. In sporadic triplenegative breast cancer, dysregulation of *BRCA1*, a protein with critical roles in the homologous recombination-dependent DNA-repair pathway, has been attributed to a number of mechanisms, including *BRCA1*-promoter methylation and overexpression of the negative regulators *ID4* and *HMG*.^[21-24]

Poly (adenosine diphosphate-ribose) polymerase 1 (PARP1), an important regulator of the DNA base-excision-repair pathway, has emerged as a therapeutic target for triple-negative breast cancer. Preclinical studies have shown that combining PARP1 inhibitors with platinum chemotherapy agents, which induce DNA damage through adducts and cross-linking, potentiates chemotherapeutic cytotoxicity.^[25,26]

Pathologic and molecular features of triple-negative breast cancer

Triple-negative breast cancer has both unique pathologic and molecular characteristics.^[27-29] Although frequently referred to interchangeably, it is important to clarify that the terms “triple negative” and “basal-like” are not completely synonymous, illustrating an approximately 20%–30% discordance across several studies.^[28,30-32] The term triple negative refers to the immunohistochemical classification of breast tumors lacking ER, PgR, and HER2 protein expression, whereas the basal-like subtype is defined via gene expression microarray analysis.^[19,27] To date, the basal-like classification is available only in the research setting; thus, the triple-negative phenotype currently serves as a reliable surrogate in the clinical arena.

Association between the triple-negative phenotype and breast cancers harboring germline mutations in the *BRCA1* gene has been well-described. The *BRCA1* gene, located on chromosome 17 (17q21) and often termed the “caretaker of the genome,” is responsible for both inherent DNA damage-sensing processes and DNA repair mechanisms. Mutations in this important gene confer an approximately 80% lifetime risk of breast cancer among carriers.^[32,33] The large majority of *BRCA1*-associated breast cancers express the triplenegative phenotype in addition to “basal-like” cytokeratins (CK 5, 14, 17) and *HER1/EGFR*.^[34-37] In addition, gene expression studies further support this connection, because *BRCA1*-mutated breast tumors typically cluster within the basal-like subtype.^[38]

Principles of treatment

Although mTNBC encompasses a unique subset of patients, the therapeutic approach mimics that of other subsets of patients with mBC. As opposed to patients with localized breast cancer where the primary goal of treatment is cure, treatment of mBC focuses on prolonging the progression-free

survival (PFS) and OS and improving the quality of life (QOL) through the reduction or stabilization of tumor burden and other cancer-related symptoms.^[39-41]

Given the lack of prospective data showing an improvement in OS among patients with mBC who are treated with combination rather than single-agent chemotherapy^[42] and the lack of a well-validated, consensus-derived surrogate endpoint,^[43] the choice between chemotherapy strategies is typically dependent upon many factors, including the degree of tumor burden, rate of disease progression, site of metastasis, organ involvement and function, cancer-related symptoms, and residual toxicities from prior therapies.^[44] Taking these variables into account, clinicians often use combination chemotherapy in mBC only when it has been determined that the patient is in need of significant treatment response or stabilization in a relatively short amount of time.^[45] While minimizing the burden of disease outside the CNS reduces the risk of CNS metastases, systemic chemotherapy is relatively ineffective at treating CNS disease.

Single-agent chemotherapy

Due to the lack of high-quality comparative data, the most efficacious sequencing of chemotherapy agents in the treatment of mTNBC has yet to be defined. Despite several head-to-head chemotherapy trials within the metastatic setting, much of what is applied in clinical practice is extrapolated from chemotherapy trials in the adjuvant setting, with taxanes and anthracyclines incorporated early in the patient's treatment course (granted, they had not received similar therapy in the adjuvant setting).

Microtubule inhibitors

The class of chemotherapy agents commonly referred to as taxanes are among the most commonly used agents in mTNBC, especially when used as a single agent, and this class consists of drugs, such as docetaxel, paclitaxel, and nab-paclitaxel.

Anthracyclines

Chemotherapy agents included within this class are doxorubicin and epirubicin, both of which are generally administered every three weeks,^[46-48] and pegylated liposomal doxorubicin, which is typically given every four weeks.^[45,48]

Antimetabolites/others

Capecitabine, a 5-fluorouracil (5-FU) prodrug and pyrimidine antimetabolite that inhibits thymidylate synthetase, is an oral chemotherapy agent administered on a two-week-on/one-week-off schedule.^[49-51]

Combination chemotherapy

Combination chemotherapy is uncommonly used in the treatment of mTNBC, but select combinations have been shown to be effective in producing swifter and more significant responses compared with single-agent chemotherapy. Notably, at the expense of tolerability and to our knowledge, there are no data demonstrating an improvement in patient survival using combination rather than single-agent therapy prescribed in a sequential fashion. However, several combinations of systemic chemotherapy have been associated with improved survival outcomes in the metastatic setting compared with non sequential single-agent therapy alone.

Although more toxic than sequential single-agent treatment or nonanthracycline-containing combinations, anthracycline-based chemotherapy regimens are associated with an ORR of ~60% in previously untreated patients with mBC. In a

meta-analysis of eight trials and 3,000 patients looking at taxane plus anthracycline regimens compared with nontaxane anthracycline-containing combinations, an anthracycline plus taxane combination resulted in a higher ORR (57% vs 46%) but no difference in OS.^[52] Other anthracycline-based regimens include doxorubicin plus cyclophosphamide (ORR: 47%–54%, OS: 21.5 months),^[53] epirubicin with cyclophosphamide and fluorouracil (ORR: 45%–55%, OS: 18.9 months),^[54] doxorubicin with docetaxel plus cyclophosphamide (ORR: 77%, OS: 20.5 months),^[55] and doxorubicin plus paclitaxel or docetaxel (ORR: 40%, OS: 20.6 months).^[56]

Future directions

The epidermal growth factor receptor (EGFR) is commonly over expressed in mTNBC. However, three Phase II clinical trials evaluating the efficacy of the anti-EGFR monoclonal antibody cetuximab in combination with chemotherapy demonstrated only a modest beneficial treatment effect.^[57-59]

Polyadenosine diphosphate-ribose polymerase (PARP) is involved in the molecular events leading to cell recovery from DNA damage. If PARP1 is inhibited under normal conditions, double-strand DNA breaks accumulate and are repaired via the BRCA pathway-dependent homologous recombination mechanism.^[60-62]

PARP inhibitors, currently only FDA approved for advanced ovarian cancer, are a class of agents that are commonly tested within the context of a clinical trial in mTNBC,^[63] especially among those with a mutation in BRCA.

Conclusion

The management of patients with mTNBC can be quite complex and often requires consideration of many different patient-, tumor-, and therapy-related factors in order to tailor the treatment and optimize the care. The expert group of oncologist discussed on the options available to treat patients with mTNBC undergoing chemotherapy or targeted therapy. Although there have been many new agents approved for mBC over the past 20 years, the treatment options for the subset of patients with mTNBC remain somewhat limited. The decisions of expert to select synergistic combinations which can produce faster and more significant response rates compared with monotherapy and are typically used in the setting of visceral threat or symptomatic disease. In conclusion of this discussion underway assessing new chemotherapeutic strategies and agents, including targeted therapy and immunotherapy to evaluate the standard systemic and best treatment options in mTNBC.

Take Home Message

1. Post BCS radiation therapy can be given to patients with early node positive (pT1N1) breast cancers
2. Hypofractionation can be given to patients based on recent reports of its equivalent efficacy in comparison with standard schedules in terms of local control and cosmesis
3. Boost is beneficial and should be given to early breast cancer patients. It has been shown to be more effective in younger patients but it is still beneficial in older patients
4. Currently there is no role for axillary radiation therapy in patients with an adequately dissected axilla
5. Internal mammary radiation may be given only to a select group of breast cancer patients. It is usually omitted in patients with significant pulmonary or cardiac concerns

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