Original Article

Practical consensus recommendations for neo-adjuvant chemotherapy in triple negative breast cancer

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Abstract

This manuscript provides a practical and easy to use consensus recommendation to community oncologists on how to use neoadjuvant chemotherapy in triple negative breast cancer patients.

Key words: Anthracycline, BCS, BRCA, carboplatin, elderly, radiotherapy, SLNB, taxane, tumor size

Introduction

Neo-adjuvant chemotherapy is indicated in patients with locally advanced breast cancers or those patients in whom upfront breast conservation surgery is not possible. Patients with triple negative early breast cancers can also be offered neo-adjuvant chemotherapy, as disease free survival and overall survival benefit has been associated with achievement of pathological complete response (pCR) after the same[1-3]

The expert group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines on the management of operable triple negative breast cancer. This manuscript is the outcome of the expert group discussion and consensus arrived at in May 2017.

Defining Clinical Cohort and Practice of Expert Group Panel Members

The primary objective was to provide a consensus statement for community oncologists that could be applicable as ready-to-use practical recommendations. Hence, the applicable setting was outlined by defining the clinical cohort and current practice of the participating delegates and expert group panel members – on the basis of which this document was prepared.

The expert group discussed a hypothetical clinical scenario of a 40 year old premenopausal lady diagnosed with non metastatic infiltrating duct carcinoma and a palpable axillary lymph node. A series of questions on key practical issues and management challenges were asked, with each question answerable in the form of selection from multiple choice options. The consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements [Table 1].

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Role of BRCA Testing and Chemotherapy Regimens Used

The panel recommended that patients with TNBC and tumor size T2 or bigger should receive NACT followed by surgery, as disease free survival and overall survival benefit has been associated with achievement of pathological complete response (pCR) after chemotherapy.[1-3] The members of the audience also unanimously agreed with the same [Table 2].

BRCA mutations are found to the tune of 20% in patients with TNBC.[4] In another study of 1,824 patients unselected for family history of breast or ovarian cancer who were tested for mutations in 17 breast cancer susceptibility genes, 8.5% patients were found to have mutations in the BRCA1 gene and 2.7% patients had mutations in the BRCA2 gene. The study also noted that those patients with mutations were diagnosed at an earlier age and had higher-grade tumors than those without mutations.[5] The expert opinion was divided about the need for genetic counselling and BRCA testing in patients with TNBC. The panel recommended following the NCCN guidelines, and getting patients 60 years of age or less tested for BRCA mutations after proper counselling and consent.[6] The attending oncologists also agreed with the same [Table 3].

In the Cancer and Leukemia Group B (CALGB) 40603 study, addition of carboplatin to standard dose dense doxorubicin, cyclophosphamide and weekly paclitaxel based NACT in patients with TNBC was associated with increased pathological CR rates (60% versus 44%). However, this was also associated with increased toxicities, leading to a higher frequency of treatment interruption and discontinuation.[7] Similar findings were seen in the GeparSixto study. Patients with TNBC who received carboplatin in the neoadjuvant setting had path CR rates of 53%, compared with 37% in those patients who did not, with increased toxicities and treatment interruptions.[8] The study showed a 10 percent absolute improvement in EFS with addition of carboplatin, however a similar benefit was not observed in the CALGB trial. After discussing the available evidence, the experts were divided regarding the addition of carboplatin to standard taxane based neo-adjuvant chemotherapy in patients with operable breast cancer. The

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members of the audience were similarly divided, as seen in Table 4. The panel recommends standard NACT in patients with TNBC until further data is available. However the experts recommend adding carboplatin to paclitaxel in patients who have a less than optimal response to anthracycline based chemotherapy.

Arun *et al*. studied 317 patients receiving NACT and found that pathological CR percentage was higher in patients with BRCA 1 carriers as compared to BRCA non carriers. The study also noted that statistically significant higher overall survival and relapse free survival were seen in patients who achieved a pCR than patients who did not.[9] In another study including 102 patients with BRCA 1 mutation, it was found that 83% of the patients experienced a pathological CR after treatment with cisplatin as opposed to 8% patients who received doxorubicin and docetaxel and 22% patients who received cyclophosphamide, doxorubicin and/or fluorouracil.[10] Data from a recent stage three randomised study ofpatients in the recurrent/metastatic setting found no survival benefit of carboplatin over docetaxel in patients with TNBC. However, those patients who had a BRCA mutation, had an improved objective response rate with carboplatin (68% versus 30% with docetaxel).[11] Keeping this evidence in view, the panel was divided regarding the addition of carboplatin to taxane based therapy in patients who were BRCA mutation positive. The audience was similarly divided [Table 5].

Patients undergoing chemotherapy should be evaluated before each cycle to document response and detect clinical progression.

Table 1: Question categories addressed by the expert panel

Broad question title	Number of sub questions
Optimum treatment of operable TNBC	1
Role of BRCA testing in TNBC	1
Radiotherapy in TNBC	1
Surgery in TNBC	3
Chemotherapy in TNBC	2

TNBC=Triple negative breast cancer

Table 2: Question 1 - In a 40-year-old premenopausal lady with triple negative, clinically node positive operable breast cancer what would be the primary treatment approach?

Options	Surgery	NACT
Percentage of polled oncologists	0	100

Expert group consensus: NACT recommended inpatients with TNBC and tumour size T2 or bigger. NACT=Neoadjuvant chemotherapy, TNBC=Triple negative breast cancer

Table 3: Question 2 - In a 40-year-old premenopausal lady with triple negative operable breast cancer, is BRCA testing indicated?

Options	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: Patients with TNBC who are 60 years of age or less, should be tested for BRCA mutations. TNBC=Triple negative breast cancer

Table 4: Question 3 - In a 40-year-old premenopausal lady with triple negative, clinically node negative operable breast cancer, what chemotherapy protocol is preferred in the neoadjuvant setting?

Options	Platinum containing regimen	Taxane containing regimen
Percentage of polled oncologists	40	60

Expert group consensus: Standard anthracycline and taxane based regimens are recommended

Management of the axilla

The panel opined that SLNB in patients who were initially clinically node positive, and had a good response to chemotherapy is a viable option. The attending oncologists also agreed with the same, as reflected by the poll results [Table 6]. This recommendation was based on a study which enrolled 143 patients with FNAC proven positive axillary nodes, who then received NACT and underwent sentinel node biopsy. The sentinel lymph node could be identified in 130 cases (90.9%); the false negative rate (FNR) was 16.0%. The FNR was 10.5% for patients with TNBC.[12] Similarly, a meta-analysis of 7400 women with locally advanced breast cancer who underwent SLNB after NACT, showed the sentinel node identification rate to be 89.6 percent and the FNR to be 14.2 percent.[13] Radiological and pathological axillary staging should be performed before NACT to confirm involvement. The involved node should be marked with a clip. The experts recommended axillary clearance in case of node positivity after SLNB, and most of the audience agreed with the recommendation [Table 7].

Surgery and radiotherapy

The panel recommended breast conservation surgery followed by post operative RT wherever feasible for patients who are BRCA mutation negative and B/L mastectomy for those patients who are BRCA positive. The attending oncologists were of a similar opinion [Table 8].

The experts recommended radiotherapy planning as per pre NACT tumour and nodal status [Table 9].

Take Home Message

- The panel recommends that patients with TNBC and tumour size T2 or bigger should receive NACT followed by surgery
- The panel recommends getting patients 60 years of age or less diagnosed with TNBC, tested for BRCA mutations after proper counseling and consent
- The panel recommends standard anthracycline and taxane based regimens for patients with TNBC
- The panels recommends adding carboplatin to paclitaxel in patients who have a less than optimal response to anthracycline based chemotherapy
- The panel was divided regarding the addition of carboplatin to taxane based therapy in patients who were BRCA mutation positive
- The panel recommends doing SLNB in patients who were initially clinically node positive, and have a good response to chemotherapy, with radiological axillary staging wherever needed
- The panel recommends axillary clearance in case of node positivity after SLNB
- The panel recommends breast conservation surgery followed by post operative RT wherever feasible for patients who are BRCA mutation negative, and B/L mastectomy for those patients who are BRCA positive

Table 5: Question 4: In a 40-year-old premenopausal lady with triple negative, clinically node negative operable breast cancer, who is positive for the BRCA gene mutation, what chemotherapy protocol is preferred in the neoadjuvant setting?

Options	Platinum containing regimen	Taxane containing regimen
Percentage of polled oncologists	75	25

Expert group consensus: Standard anthracycline and taxane based regimens are recommended, until further evidence is available

Table 6: Question 5 - In a 40-year-old premenopausal lady with triple negative, operable breast cancer, should sentinel node biopsy be performed following neoadjuvant chemotherapy?

Options	Yes	No
Percentage of polled oncologists	100	0

Expert group consensus: SLNB may be feasible in patients who were initially clinically node positive, and have a good response to chemotherapy (axillary radiology imaging to be used as appropriate). SLNB=Sentinel lymph node biopsy

Table 7: Question 6 - In a 40-year-old premenopausal lady with triple negative, operable breast cancer, if sentinel node biopsy is positive, should axillary dissection be performed?

Options	Yes	No
Percentage of polled oncologists	75	25

Expert group consensus: Axillary clearance, in case of node positivity, after SLNB, is recommended. SLNB=Sentinel lymph node biopsy

Table 8: Question 7 - In a 40-year-old premenopausal lady with triple negative, operable breast cancer, who has responded to neoadjuvant chemotherapy, what would be the preferred surgery?

Options	MRM	BCS
Percentage of polled oncologists	0	100

Expert group consensus: Breast conservation surgery followed by postoperative radiotherapy wherever feasible for patients who are BRCA mutation negative

Table 9: Question 8 - In a 40-year-old premenopausal lady with triple negative, operable breast cancer, who has received neoadjuvant chemotherapy, how is the approach to radiotherapy decided?

Options	As per pre-NACT status	As per post-NACT status
Percentage of polled oncologists	0	100

Expert group consensus: Radiotherapy planning as per pre-NACT tumour and nodal status. NACT=Neoadjuvant chemotherapy

- The panel recommends radiotherapy planning as per pre NACT tumour and nodal status.

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Conflicts of interest

There are no conflicts of interest.

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