Original Article

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

R. Rangarao, B. K. Smruti[1], K. Singh[2], A. Gupta[3], S. Batra, R. K. Choudhary[4], A. Gupta[5], S. Sahani[6], Vedant Kabra[7], Purvish M. Parikh[8], S. Aggarwal[9]

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 1 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 discus 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

Access this article online

Quick Response Code:

Website: www.sajc.org

DOI: 10.4103/sajc.sajc_118_18

Department of Medical Oncology, Max Hospital, [2]Department of Radiation Oncology, MAMC, [3]Department of Radiation Oncology, Safdarjung Hospital, [4]Department of Medical Oncology, Metro Cancer Center, [6]Department of Surgical Oncology, Indraprastha Apollo Hospital, [9]Department of Medical Oncology, Sir Ganga Ram Hospital, New Delhi, [8]Department of Oncology, Shalby Cancer and Research Institute, [1]Dept of Medical Oncology, Bombay Hospital, Mumbai, Maharashtra, [5]Department of Radiation Oncology, GMC, Jammu and Kashmir, [7]Department of Surgical Oncology, Manipal Super Specialty Hospital, Gurugram, Haryana, India

Correspondence to: Dr. R. Rangarao, E-mail: rangaraorr@gmail.com

How to cite this article: Rangarao R, Smruti BK, Singh K, Gupta A, Batra S, Choudhary RK, *et al*. Practical consensus recommendations on management of triple-negative metastatic breast cancer. South Asian J Cancer 2018;7:127-31.

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 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.

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

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 homologousrecombination–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

	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

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7-30.
2. Zeichner SB, Ambros T, Zaravinos J, Montero AJ, Mahtani RL, Ahn ER, *et al.* Defining the survival benchmark for breast cancer patients with systemic relapse. Breast Cancer (Auckl) 2015;9:9-17.
3. Zeichner SB, Herna S, Mani A, Ambros T, Montero AJ, Mahtani RL, *et al.* Survival of patients with *de-novo* metastatic breast cancer: Analysis of data from a large breast cancer-specific private practice, a university-based cancer center and review of the literature. Breast Cancer Res Treat 2015;153:617-24.
4. Mersin H, Yildirim E, Berberoglu U, Gülben K. The prognostic importance of triple negative breast carcinoma. Breast 2008;17:341-6.
5. Dawood S, Lei X, Litton JK, Buchholz TA, Hortobagyi GN, Gonzalez-Angulo AM, *et al.* Incidence of brain metastases as a first site of recurrence among women with triple receptor-negative breast cancer. Cancer 2012;118:4652-9.
6. Lin NU, Vanderplas A, Hughes ME, Theriault RL, Edge SB, Wong YN, *et al.* Clinicopathologic features, patterns of recurrence, and survival among women with triple-negative breast cancer in the National Comprehensive Cancer Network. Cancer 2012;118:5463-72.
7. National Cancer Registry Programme, Indian Council of Medical Research. Leading Sites of Cancer. In, Consolidated Report of Population Based Cancer Registries 2001-2004, Incidence and Distribution of Cancer. Bangalore: Coordinating Unit, National Cancer Registry Programme (ICMR); 2006. p. 8-30.
8. Badwe RA, Gangawal S, Mittra I, Desai PB. Clinico-pathological features and prognosis of breast cancer in different religious communities in India. Indian J Cancer 1990;27:220-8.
9. Altekruse SF, Kosary CL, Krapcho M, editors. SEER Cancer Statistics Review 1975-2007. SEER Cancer Statistics Review. National Cancer Institute.
10. National Cancer Registry Program. Ten Year Consolidated Report of the Hospital Based Cancer Registries, 1984–1993, an Assessment of the Burden and Care of Cancer Patients. New Delhi: Indian Council of Medical Research; 2001.
11. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. World J Surg 2007;31:1031-40.
12. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, *et al.* Race, breast cancer subtypes, and survival in the Carolina breast cancer study. JAMA 2006;295:2492-502.
13. Osborne CR, Kannan L, Ashfaq R, Ariyibi J, Frawley WH, Tripathy D. Clinical and Pathological Characterization of Basal-Like Breast Cancer. Presented at the San Antonio Breast Cancer Symposium, San Antonio, TX; December 8–11, 2005.
14. Dent R, Hanna WM, Trudeau M, Rawlinson E, Sun P, Narod SA, *et al.* Pattern of metastatic spread in triple-negative breast cancer. Breast Cancer Res Treat 2009;115:423-8.
15. Rodríguez-Pinilla SM, Sarrió D, Honrado E, Hardisson D, Calero F, Benitez J, *et al.* Prognostic significance of basal-like phenotype and fascin expression in node-negative invasive breast carcinomas. Clin Cancer Res 2006;12:1533-9.
16. Rouzier R, Perou CM, Symmans WF, Ibrahim N, Cristofanilli M, Anderson K, *et al.* Breast cancer molecular subtypes respond differently to preoperative chemotherapy. Clin Cancer Res 2005;11:5678-85.
17. Parker JS, Mullins M, Cheang MC, Leung S, Voduc D, Vickery T, *et al.* Supervised risk predictor of breast cancer based on intrinsic subtypes. J Clin Oncol 2009;27:1160-7.
18. Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, *et al.* Survival outcomes for patients with metastatic triple-negative breast cancer: Implications for clinical practice and trial design. Clin Breast Cancer 2009;9:29-33.
19. Sorlie T, Tibshirani R, Parker J, Hastie T, Marron JS, Nobel A, *et al.* Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci U S A 2003;100:8418-23.
20. Swain SM. Triple-Negative Breast Cancer: Metastatic Risk and Role of Platinum Agents. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, May 30–June 03, 2008.
21. Baldassarre G, Battista S, Belletti B, Thakur S, Pentimalli F, Trapasso F, *et al.* Negative regulation of BRCA1 gene expression by HMGA1 proteins accounts for the reduced BRCA1 protein levels in sporadic breast carcinoma. Mol Cell Biol 2003;23:2225-38.
22. Beger C, Pierce LN, Kruger M, Marcusson EG, Robbins JM, Welcsh P, *et al.* Identification of id4 as a regulator of BRCA1 expression by using a ribozyme-library-based inverse genomics approach. Proc Natl Acad Sci U S A 2001;98:130-5.
23. Esteller M, Silva JM, Dominguez G, Bonilla F, Matias-Guiu X, Lerma E, *et al.* Promoter hypermethylation and BRCA1 inactivation in sporadic breast and ovarian tumors. J Natl Cancer Inst 2000;92:564-9.
24. Turner NC, Reis-Filho JS, Russell AM, Springall RJ, Ryder K, Steele D, *et al.* BRCA1 dysfunction in sporadic basal-like breast cancer. Oncogene 2007;26:2126-32.
25. Alli E, Sharma VB, Sunderesakumar P, Ford JM. Defective repair of oxidative dna damage in triple-negative breast cancer confers sensitivity to inhibition of poly (ADP-ribose) polymerase. Cancer Res 2009;69:3589-96.
26. Ossovskaya V, Li L, Broude EV. BSI-201 Enhances the Activity of Multiple Classes of Cytotoxic Agents and Irradiation in Triple Negative Breast Cancer. Abstract 5552. In: Program and Abstracts of the American Association for Cancer Research Annual Meeting Denver, April 18–22, 2009.
27. Sørlie T, Perou CM, Tibshirani R, Aas T, Geisler S, Johnsen H, *et al.* Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98:10869-74.
28. Nielsen TO, Hsu FD, Jensen K, Cheang M, Karaca G, Hu Z, *et al.* Immunohistochemical and clinical characterization of the basal-like subtype of invasive breast carcinoma. Clin Cancer Res 2004;10:5367-74.
29. Livasy CA, Karaca G, Nanda R, Tretiakova MS, Olopade OI, Moore DT, *et al.* Phenotypic evaluation of the basal-like subtype of invasive breast carcinoma. Mod Pathol 2006;19:264-71.
30. Bertucci F, Finetti P, Cervera N, Esterni B, Hermitte F, Viens P, *et al.* How basal are triple-negative breast cancers? Int J Cancer 2008;123:236-40.
31. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: Therapeutic options. Lancet Oncol 2007;8:235-44.
32. Kreike B, van Kouwenhove M, Horlings H, Weigelt B, Peterse H, Bartelink H, *et al.* Gene expression profiling and histopathological characterization of triple-negative/basal-like breast carcinomas. Breast Cancer Res 2007;9:R65.
33. Narod SA. Modifiers of risk of hereditary breast and ovarian cancer. Nat Rev Cancer 2002;2:113-23.
34. Narod SA, Foulkes WD. BRCA1 and BRCA2: 1994 and beyond. Nat Rev Cancer 2004;4:665-76.
35. Arnes JB, Brunet JS, Stefansson I, Bégin LR, Wong N, Chappuis PO, *et al.* Placental cadherin and the basal epithelial phenotype of BRCA1-related breast cancer. Clin Cancer Res 2005;11:4003-11.
36. Foulkes WD, Stefansson IM, Chappuis PO, Bégin LR, Goffin JR, Wong N, *et al.* Germline BRCA1 mutations and a basal epithelial phenotype in breast cancer. J Natl Cancer Inst 2003;95:1482-5.
37. Laakso M, Loman N, Borg A, Isola J. Cytokeratin 5/14-positive breast cancer: True basal phenotype confined to BRCA1 tumors. Mod Pathol 2005;18:1321-8.
38. Lakhani SR, Reis-Filho JS, Fulford L, Penault-Llorca F, van der Vijver M, Parry S, *et al.* Prediction of BRCA1 status in patients with breast cancer using estrogen receptor and basal phenotype. Clin Cancer Res 2005;11:5175-80.
39. Stockler M, Wilcken NR, Ghersi D, Simes RJ. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. Cancer Treat Rev 2000;26:151-68.
40. Osoba D. Health-related quality of life as a treatment endpoint in metastatic breast cancer. Can J Oncol 1995;5 Suppl 1:47-53.
41. Geels P, Eisenhauer E, Bezjak A, Zee B, Day A. Palliative effect of chemotherapy: Objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. J Clin Oncol 2000;18:2395-405.
42. Dear RF, McGeechan K, Jenkins MC, Barratt A, Tattersall MH, Wilcken N, *et al.* Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev 2013;CD008792.
43. Burzykowski T, Buyse M, Piccart-Gebhart MJ, Sledge G, Carmichael J, Lück HJ, *et al.* Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. J Clin Oncol 2008;26:1987-92.
44. Robertson JF, Howell A, Buzdar A, von Euler M, Lee D. Static disease on anastrozole provides similar benefit as objective response in patients with advanced breast cancer. Breast Cancer Res Treat 1999;58:157-62.
45. Carrick S, Parker S, Thornton CE, Ghersi D, Simes J, Wilcken N, *et al.* Single agent versus combination chemotherapy for metastatic breast

cancer. Cochrane Database Syst Rev 2009;CD003372.
46. O'Brien ME, Wigler N, Inbar M, Rosso R, Grischke E, Santoro A, *et al.* Reduced cardiotoxicity and comparable efficacy in a phase III trial of pegylated liposomal doxorubicin HCl (CAELYX/Doxil) versus conventional doxorubicin for first-line treatment of metastatic breast cancer. Ann Oncol 2004;15:440-9.
47. Keller AM, Mennel RG, Georgoulias VA, Nabholtz JM, Erazo A, Lluch A, *et al.* Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. J Clin Oncol 2004;22:3893-901.
48. Piccart-Gebhart MJ, Burzykowski T, Buyse M, Sledge G, Carmichael J, Lück HJ, *et al.* Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. J Clin Oncol 2008;26:1980-6.
49. Fumoleau P, Largillier R, Clippe C, Dièras V, Orfeuvre H, Lesimple T, *et al.* Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 2004;40:536-42.
50. Oshaughnessy JA, Blum J, Moiseyenko V, Jones SE, Miles D, Bell D, *et al.* Randomized, open-label, phase II trial of oral capecitabine (Xeloda) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouracil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001;12:1247-54.
51. Ambros T, Zeichner SB, Zaravinos J, Montero AJ, Ahn E, Aruna M, *et al.* A retrospective study evaluating a fixed low dose capecitabine monotherapy in women with HER-2 negative metastatic breast cancer. Breast Cancer Res Treat 2014;146:7-14.
52. Baselga J, Gomez P, Awada A. The Addition of Cetuximab to Cisplatin Increases Overall Response Rate and Progression-Free Survival ini Metastatic Triple Negative Breast Cancer: Results of a Randomized Phase II Study (abstract 2740). Data Presented at the 2010 Meeting of the European Society of Medical Oncology. Milan, Italy; 2010. Available from: http://www.annonc.oxfordjournals.org/content/21/suppl_8. [Last accessed on 2011 Sep 07].
53. O'Shaughnessy J, Weckstein D, Vukelja S. Preliminary Results of a Randomized Phase II Study of Weekly Irinotecan/Carboplatin with or Without Cetuximab in Patients with Metastatic Breast Cancer. Abstract 308. San Antonio Breast Cancer Symposium; 2007.
54. Carey LA, Rugo HS, Marcom PK, Mayer EL, Esteva FJ, Ma CX, *et al.* TBCRC 001: Randomized phase II study of cetuximab in combination with carboplatin in stage IV triple-negative breast cancer. J Clin Oncol 2012;30:2615-23.
55. Tentori L, Graziani G. Chemopotentiation by PARP inhibitors in cancer therapy. Pharmacol Res 2005;52:25-33.
56. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, *et al.* Specific killing of BRCA2-deficient tumours with inhibitors of poly (ADP-ribose) polymerase. Nature 2005;434:913-7.
57. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, *et al.* Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005;434:917-21.
58. ClinicalTrials.gov. Metastatic Triple Negative Breast Cancer. National Institutes of Health; 2015. Available from: https://www.clinicaltrials.gov. [Last accessed on 2015 Oct 20].
59. Jones S, Winer E, Vogel C, Laufman L, Hutchins L, O'Rourke M, *et al.* Randomized comparison of vinorelbine and melphalan in anthracycline-refractory advanced breast cancer. J Clin Oncol 1995;13:2567-74.
60. Nabholtz JM, Falkson C, Campos D. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: Results of a randomized, multicenter, phase III trial. J Clin Oncol 2003;21:968.
61. Biganzoli L, Cufer T, Bruning P, Coleman R, Duchateau L, Calvert AH, *et al.* Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 Multicenter Phase III Trial. J Clin Oncol 2002;20:3114-21.
62. Nabholtz JM, Mackey JR, Smylie M, Paterson A, Noël DR, Al-Tweigeri T, *et al.* Phase II study of docetaxel, doxorubicin, and cyclophosphamide as first-line chemotherapy for metastatic breast cancer. J Clin Oncol 2001;19:314-21.
63. Cassier PA, Chabaud S, Trillet-Lenoir V, Peaud PY, Tigaud JD, Cure H, *et al.* A phase-III trial of doxorubicin and docetaxel versus doxorubicin and paclitaxel in metastatic breast cancer: Results of the ERASME 3 study. Breast Cancer Res Treat 2008;109:343-50.