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Update on Treatment Protocols in Breast Carcinoma

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ABSTRACT: The treatment protocols of carcinoma is dependent upon disease staging, tumor characteristics such as- metastasis, status of molecular markers like ER, PR and HER2 new. Treatment protocols involve, surgery, chemotherapy and radiotherapies and combinations of all three. This review article deals with various chemotherapeutic protocols which are being tested under various clinical trials and their mechanisms of actions. Standard chemotherapy treatments lack the ability to distinguish between healthy cells and cancerous cells. As a result, they can lead to significant side effects that are frequently more distressing than the actual cancer. Also, recent advancement as immunotherapy inclusion has also been included. We will now provide an overview of the ongoing efforts in developing dynamic biomarkers for treatment response.

Keywords: Breast carcinoma, chemotherapy, protocols, treatment. Modified radical mastectomies, breast conserving surgeries, oncoplastic breast surgery.

INTRODUCTION

Breast carcinoma is a leading cause of death in less-developed countries. The incidence of breast carcinoma is 25% higher in developing countries when compared to developed nations. It varies widely among different populations. Women in western Europe and United States have a very high incidence then women in the most of the other parts of the world, possibly in part because of high intake of animal proteins and fat and probably linked to the high caloric intake and increase rate of obesity. Caucasian women in USA are more likely to develop breast cancer compared with African American women. Breast carcinoma therapy is dependent upon disease staging and tumor characteristics. Treatment involves chemotherapy, surgery, radiation and hormonal therapies (Albain *et al.*, 2008).

Administration of chemotherapeutic drugs before surgery is known as 'neoadjuvant chemotherapy' and is the standard protocol for locally advanced disease. The most commonly used chemotherapy agents include- Anthracycline and Taxanes. Anthracycline include drugs such as- Doxorubicin and Epirubicin while Taxanes include- Paclitaxel and Docetaxel. Additionally, these agents are used in combination with other agents such as Cyclophosphamide and Fluorouracil (Buzdar *et al.*, 2002).

SCREENING DIAGNOSIS AND PRETREATMENT EVALUATION

Screening- Because the more and more lives can be saved by early diagnosis. the standard protocol for the breast cancer screening is- 1, monthly breast examination after puberty and yearly breast examination after 20 years of age. 2, mammography- It reduces the mortality by 25 % to 30 % in women older than 50 years. It should be done by an experienced physician at the age of 40 years as a baseline, every 1 to 2 years between the age of 40 to 50 years and every year after 50 years of age.

Outcomes in breast carcinoma – depends upon the stage of disease

The standard TNM classification for the stage is usually done before starting any treatment of breast cancer. Although the definite stage is done after surgery, which helps in planning further treatment and explaining the prognosis of disease.

The standard protocol for proper staging of this disease is PET CT scan. It can detect the distant metastasis and accurate local and regional metastasis of carcinoma of breast.

Evaluations of clinical outcomes in breast carcinoma is generally assessed on basis of following parameters such as-

I. Primary outcomes (Buzdar *et al.*, 2002):

(a) Pathological complete response: It is defined as 'complete response of primary or axillary lymph nodes or both' (Buzdar *et al*., 2002).
(b) Overall response: It is defined as 'complete disappearance of clinically palpable tumor (complete clinical response) or >50% reduction in tumor volume (clinical partial response) (Buzdar *et al*., 2002).

II. Secondary outcomes: These include (Buzdar et al., 2002)

(a) Clinical complete response: It is defined as 'complete disappearance of clinically palpable tumor' (Buzdar *et al*., 2002).
(b) Pathological complete response of primary with ductal carcinoma in situ: It is defined as 'complete response of primary regardless of axilla but allowing for ductal carcinoma in situ' (Buzdar *et al*., 2002).
(c) Loco-regional recurrence: It is defined as 'carcinoma recurrence in local or regional area' (Buzdar *et al*., 2002).
(d) Distant metastasis: it is defined as 'time from randomization to carcinoma in local or distant sites' (Buzdar *et al*., 2002).
(e) Disease-free survival: It is defined as 'time from randomization to carcinoma recurrence in local or distantsites' (Buzdar *et al*., 2002).
(f) death due to any cause' (Buzdar *et al*., 2002).

Standard treatment protocols

1. Stage one tumor- Quadrantectomy + axillary lymphnode dissection + chemotherapy + radiotherapy. (Breast conserving surgery)
2. Modified radical mastectomy + breast reconstruction+ CCT + RT.
3. Stage 2 and 3- Modified radical mastectomy + CCT + RT. Age less than 45 years- hormonal manipulation by ovarian ablation either by RT or surgical.
4. Stage 4 locally advanced cancer- Neo adjuvant chemotherapy+ simple mastectomy+ axillary lymph node dissection if lymph nodes are not fixed + RT + hormonal treatment.
5. Metastatic breast cancer- chemotherapy+ targeted Chemotherapy+ palliative RT (for bony pains or for control of locally advanced disease.

Selection of chemotherapeutic agents against breast carcinoma. The treatment choice in advanced breast carcinoma is governed by ESO-ESMO second international consensus guidelines. These are governed by various factors like- tumor biology (hormonal receptor and HER2 expression) and subject characteristics such as- age, menopausal status and comorbidities.

Those triple-negative breast carcinoma cases which lack therapeutic targets, chemotherapy remains the main mode of treatment (Cardoso *et al*., 2016).

In HER2-positive subjects, treatment depends on HER2 blockade. Most commonly utilized treatment strategies include- HER2-target agents along with combination of chemotherapy via oral or intravenous route and/or hormonal therapy.

Though the treatment duration and response rates reduce as numbers of lines of therapy increase much beyond the first-line drug regimen.

Selection of chemotherapy agents is not tailored as per molecular profiles except in case of Platinum-based agents for BRCA-associated breast carcinomas.

Both Capecitabine and Vinorelbine have demonstrated significant efficacy as well as tolerability in metastatic breast carcinoma, especially as second- and third-line therapy drugs after failure of Taxane therapy. In HER2-positive metastatic breast carcinoma cases, both Capecitabine and Vinorelbine (through i.v. route) have shown significant efficacy as well as tolerability along with HER2-targeted drugs (Cardoso *et al*., 2016).

Development of drug resistance has been reported to low-dose cyclophosphamide therapy but similar doing has been shown to be sensitive towards maximum tolerated dose in metastatic disease (Cardoso *et al*., 2016).

The standard chemotherapeutic regimen in subjects with lymph node-positive breast carcinoma is a combination of an anthracycline and a taxane (i.e., 4 cycles of doxorubicin plus cyclophosphamide (AC) which is followed by 4 cycles of Paclitaxel). Also, HER2-positive breast carcinomas are associated with better clinical responsiveness to anthracycline-based chemotherapy regimen (Cai *et al*., 2019).

Docetaxel, is the most preferred taxane in metastatic breast carcinoma cases specially in those treated with anthracycline. Both docetaxel and paclitaxel have shown to improve outcomes on incorporation with anthracycline based polychemotherapeutic protocols (Li and Li 2013; Liao *et al*., 2017).

Oral route versus intravenous routes of drug administration. Most commonly used oral chemotherapeutic agents against breast carcinoma include- Lapatinib, Everolimus and Palbociclib which significantly improve the patient outcome. Oral route bears certain advantages over intravenous route as it is more convenient and dosing can be tailor-designed as per clinician's decision. However, there are major disadvantages associated with oral route such as- dosing mistakes, when the patient forgets the treatment breaks used in some drugs (for example, 1 to 2 weeks for Capecitabine) or wrong intake of number of pills along with improper handling of drug which are in pill form. Thus, continuous patient education is important to help improve the efficacy, compliance and quality of life (Colleoni *et al*., 2002).

'Metronomic chemotherapy' is defined as- 'Administration of chemotherapy for prolonged time periods at a relatively low non-toxic dosage without long intervals of rest' (Colleoni *et al*., 2002; Monteiro *et al*., 2013; Norrby 2014; Naoum *et al*., 2018; O'Reilly *et al*., 2015).

This approach bears multiple advantages like- oral administration, ease of administration, low toxic rate, delivery of dose-dense rather than dose-intense regimens. However, oral administration of certain drugs such as- cyclophosphamide in conventional doses has certain drawbacks like- alterations in pharmacokinetics acquired resistance, increased risk of unfavourable drug interactions such as undergoing metabolism by cytochrome P34A pathway. However, oral metronomic cyclophosphamide administration has shown significant

reduction in severity of toxic side-effects whether used alone or in combination with Methotrexate (Colleoni *et al*., 2002).

Mechanisms of action. There are multiple mechanisms of action for chemotherapy which include immune system upregulation, antiangiogenic activity and direct tumor cell targeting. The antiangiogenic effects are- targeting of tumor microvasculature, increased thrombospondin (angiogenic inhibitor), apoptosis inhibition, down regulation of progenitor endothelial cell mobilization from bone marrow, targeting of cancer stem cells and hypoxia-inducible factor 1 (HIF-1α) inhibition (Cardoso *et al*., 2016).

Combination therapies. Combined metronomic drug regimens demonstrate significant activity as well as tolerability in metastatic breast carcinoma. The first such drug combination explored in metastatic breast disease was cyclophosphamide combined with methotrexate (Cardoso *et al*., 2016).

In a phase II trial, combination of oral cyclophosphamide, Capecitabine and Vinorelbine has demonstrated a complete biological response of 85% in first time diagnosed cases while a 72% response in previously treated subjects with hormone receptor positive metastatic breast carcinoma (Cardoso *et al*., 2016).

Besides this, combination with targeted agents such as- cyclophosphamide, methotrexate with Trastuzumab or Cyclophosphamide, Capecitabine and Bevacizumab have demonstrated variabilities in clinical biologic response of 46% and 68%, respectively (Cardoso *et al*., 2016; Colleoni *et al*., 2002).

On comparing the conventional treatment regimen protocol comprising of cyclophosphamide-methotrexate-5, fluorouracil, the anthracyclin-containing treatment such as- Adriamycin-Cyclophosphamide or Epirubucin Cyclophosphamide have proven to be more effective in reduction of recurrence and overall mortality rates. Additionally, inclusion of Taxanes to Anthracyclin-containing chemotherapy has also shown an increase in disease free survival rates as well as mortality (Cai *et al*., 2019).

Anthracyclin-Cyclophosphamide along with Paclitaxel-Docetaxel whether used in combination or sequential regimen demonstrates superior results when compared with Anthracyclin regimens (Li and Li 2013).

A co-administration of low-dose cyclophosphamide (CTX) and methotrexate (MTX) in pre-treated breast carcinoma subjects has demonstrated minimal toxic side-effects and reduction in neo angiogenesis. Other chemotherapeutic agents that have shown anti-tumor efficiency due to reduction in vascular endothelial growth factor (VEGF) expression (inhibiting Neovascularization) include- Doxorubicin and Paclitaxel (Liao *et al*., 2017; Monteiro *et al*., 2013).

Side-effects of chemotherapeutic agents used in treatment of breast carcinoma. The toxic chemotherapy-induced side-effects of dose-dense AC-Paclitaxel regimen include major hematological changes such as- decrease in hemoglobin, febrile neutropenia, thrombocytopenia along with other side-effects of varying organ systems such as cutaneous rash, dyspnea, pneumonia, dysphagia, peripheral neuropathy etc.[7]The severity grade of side-effects due to chemotherapeutic agents whether via oral or intravenous route outweighs the clinical benefits thereby majorly affecting the quality of life (Crown *et al*., 2014).

The incidence of side-effects such as- nausea, vomiting and mucositis due to Docetaxel is considerably less and also tolerable though chemotherapy-induced peripheral neuropathy has been observed in subjects undergoing taxane therapy (Gebbia *et al*., 2010; Li and Li 2013).

However, taxane administration such as of Docetaxel and Paclitaxel demonstrate significantly less fetal defects and other maternal complications when administered in second and third trimester of pregnancy. However, Trastuzumab use in pregnant females is associated with anhydramnios and oligohydramnios (Rasic *et al*., 2019; Sparano *et al*., 2008).

Immunotherapy in breast carcinoma. Cancer immunotherapy helps in eradicating tumor burden by remodelling the host immune system.[18,19] This approach is especially important in metastatic triple-negative breast cancer. However, the overall response rate remains low (1923%). Additionally, adverse effects such as- checkpoint inhibitions result in cardiotoxicity. Numerous viruses such as plant viruses and phages have been utilized as carriers for targeted drug delivery. Cowpea mosain virus (CPMV) has been demonstrated to induce antitumor response on their introduction into tumor microenvironment as an in situ vaccine. This virus acts by activating the innate immune response by recalibration of the host immune response (Cai *et al*., 2019) have demonstrated that a combination of CPMV with cyclophosphamide suppresses the tumor growth and inhibits lung metastasis (Tashkandi *et al*., 2015).

Hormone therapy in breast cancer- Tamoxifen 20 mg daily is recommended for 5 years in ER, PR positive patents. Other drugs -anastrozole, letrozole, exemestane, toremifene and reloxifene are used as hormone treatment.

CONCLUSIONS

Chemotherapeutic protocols in various stages of breast carcinoma are met by challenges such as induction of side effects, development of drug resistance and also, residual disease. During last few years, multiple protocols have been studied and experimented upon in form of clinical trials to test the efficacy as well as less morbid situations. Recently, immunotherapy has been ventured upon but promising results are yet to be ascertained. Thus, it remains a subject of continuous trials where the challenge of reducing the disease burden remains.

FUTURE SCOPE

Studying the updated treatment protocols in breast carcinoma will enhance treatment modalities in more effective manner.

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REFERENCES

Albain, K. S., Nag, S. M. and Calderillo-Ruiz (2008). Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracline treatment. *J Clin Oncol, 26*(24), 3950-3957.

Buzdar, A. U., Singletary, S. E., Valero, V., Booser, D. J., Ibrahim, N. K., Rahman, Z. and Theriault, R. L. (2002). Evaluation of Paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: Preliminary data of a prospective randomized trial. *Clin Cancer Res., 8,* 1073-1079.

Cardoso, F., Colleoni, M., Di, L.A., Franco, G., Gennari, A., Gugorori, J. and Llombart, A. (2016). Oral chemotherapy in advanced breast cancer: expert perspectives on its role in clinical practice. *Cancer Treatment Communications, 6*(S1), S1-10.

Colleoni, M., Rocca, A., Sandri, M. T., Zorzino, L., Masci, G., Nole, F., Peruzzoti, G. and Robertson, C. (2002). Low-dose oral methotrexate and cyclophosphamide in metastatic breast cancer: anti-tumor activity and concentration with vascular endothelial growth factor levels. *Ann Oncol, 13*, 73-80.

Crown, J., O'Leary, M. and Ooi, W. S. (2004). Docetaxel and Paclitaxel in the treatment of breast cancer: A review of clinical experience. *The Oncologist, 9*(Suppl 2), 24-32.

Cai, H., Wlbainang, C., Shukla, S. and Steinmetz, N. F. (2019). Cowpea mosaic virus immunotherapy combined with cyclophosphamide reduces breast cancer tumor burden and inhibits lung metastasis. *Adv Sci, 6*(16), 1802281.

Gebbia, V., Boussen, H. and Valerio, M. R. (2010). Oral metronomic cyclophosphamide with or without methotrexate as palliative treatment for patients with metastatic breast carcinoma. *Anticancer Res.,* 32(2), 529-536.

Li, S. G. and Li, L. (2013). Targeted therapy in HER2-positive breast cancer. *Biomed Reports, 1*, 499-505.

Liao, W. Y., Chan, T. S. and Tsai, K. K. (2017). The novel roles of stromal fibroblasts in metronomic chemotherapy. Focusing on cancer stemness and immunity. *J Can Res Prac, 4*, 123-6.

Monteiro, D. L. M., Trajano, A. J. B., Menezes, D. C. S., Silveira, N. L. M., Magalhaes, A. C., de Miranda, F. R. D. and Caldas, B. (2013). Breast cancer during pregnancy and chemotherapy: a systematic review. *Rev Assoc Med Bras, 59*(2), 174-80.

Norrby, K. (2014). Metronomic chemotherapy and anti-angiogenesis: can upgraded pre-clinical assays improve clinical trials aimed at controlling tumor growth? *APMIS, 122*, 565-579.

Naoum, G. E., Morkos, M., Kim, B. and Arafat, W. (2018). Novel targeted therapies and immunotherapy for advanced thyroid cancers. *Molecular Cancer, 17*, 51-65.

O'Reilly, E. A., Gubbin, L., Sharma, S., Tully, R., Guang, M. H. L., Weiner-Gerzel, K. and McCaffrey, J. (2015). The fate of chemoresistance in triple negative breast cancer. *BBA Clin., 3*, 257-275.

Rasic, A., Sofic, A., Beslija, S., Rasic, I. and Hasanbegovic, B. (2019). Effects of adding taxane to anthracycline-based neoadjuvant chemotherapy in locally advanced breast cancer. *Med Glas (Zenica), 16*(1), 77-82.

Sparano, J. A.,Wang, M. and Martino, S. (2008). Weekly paclitaxel in adjuvant treatment of breast cancer, *NEng J med, 358*(16), 1663-1671.

Tashkandi, E., Yan, M., Younus, J., Jawaid, M. A., Hamm, C., Kulkarni, S. and Gupta, R. (2015). Real world experience with dose dense ac-paclitaxel: Two Canadian cancer centres' experience. *J Solid Tumors, 5*(2), 86-93.

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