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Holistic Approaches in Oncotherapy

Triple Negative Breast Cancer- Overview of Therapeutic Options

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Abstract

Triple negative breast cancer (TNBC) is a heterogeneous phenotype of breast cancer characterized by the absence of estrogen receptor, progesterone receptor and overexpression of human epidermal growth factor receptor 2 (HER2) gene. In comparison to other subtypes of breast cancer, TNBCs are distinctly aggressive in nature with higher rate of recurrence and short overall survival (OS) among patients with metastasis. It presents with different clinical profile from other subtypes. Major hurdle in TNBC is its vast intertumor and intra-tumor heterogenecity and failure to identify a single unifying targetable alteration.

Because of lack of drug-targetable receptors, chemotherapy is the only recommended significant systemic treatment to improve overall and disease-free survival in TNBC. Systemic chemotherapy is a mainstay in the management of TNBC because it does not respond to hormonal or HER2 therapy. There is a controversy regarding appropriateness of the breast conserving therapy for TNBC because of its highly aggressive nature and lack of targeted therapy. TNBC exhibit more aggressive clinical behavior, metastatic pattern and worse outcome. Management of TNBC is specifically challenging one and complex as it lacks a targeted treatment approach. It implies multidisciplinary approach for improved survival including surgery, chemotherapy and radiotherapy.

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Introduction

Triple negative breast cancer (TNBC) is a heterogeneous phenotype of breast cancer characterized by the absence of estrogen receptor, progesterone receptor and overexpression of human epidermal growth factor receptor 2 (HER2) gene. TNBC accounts for 10-20% of all invasive breast cancers. It is highly aggressive subtype of breast cancer having high risk of local and distant recurrence and increased rate of mortality in first 5 years of treatment. Several clinicopathological features characterize TNBCs. Many of them have ductal origin, but other phenotypes like adenoid cystic, metaplastic, atypical or typical medullary may be present [1]. Risk factors for TNBC are young age at menarche, high parity, and full term pregnancy at young age, short duration of breast-feeding, obesity and metabolic syndrome [2].

TNBC cases are observed commonly among premenopausal women. In a systematic review, Kumar P et al reported association of TNBC with African-American race, young age, higher grade and mitotic index and advanced disease at the time of diagnosis. [3].

In comparison to other subtypes of breast cancer, TNBCs are distinctly aggressive in nature with higher rate of recurrence and short overall survival (OS) among patients with metastasis. It presents with different clinical profile from other subtypes. Hence it is an important area of focus in the field of basic as well as clinical research. Because of lack of target receptors like ER, PR and HER2, patients of TNBC do not benefit from hormonal or trastuzumab-based therapy. Surgery and chemotherapy individually or in combination remain the available therapeutic modalities for TNBC. Major hurdle in TNBC is its vast intertumor and intra-tumor heterogenecity and failure to identify a single unifying targetable alteration. TNBC grows rapidly without extensive intraductal spread. Hence breast-conserving surgery is possible in these patients. [4].

Chemotherapy

TNBC is highly aggressive heterogeneous group of disease with short disease free interval in the adjuvant and neoadjuvant settings and more aggressive progression in metastatic setting. Because of lack of drug-targetable receptors, chemotherapy is the only recommended significant systemic treatment to improve overall and disease-free survival (DFS) in TNBC. Since past few decades, aggressive chemotherapy has improved prognosis of TNBC to considerable extent. TNBC is sensitive to chemotherapy, hence patients gets complete high pathological response rate after neoadjuvant chemotherapy due to which breast conserving surgery also become possible. [3] Systemic chemotherapy is a mainstay in the management of TNBC because it does not respond to hormonal or HER2 therapy. Because of heterogeneous nature of TNBC, identification of molecular biomarkers that can predict the response to specific chemotherapy is needed to choose targeted therapy. Analyzing gene expression profiles has identified different molecular subtypes of TNBC that display unique patterns of gene expression. [5] In neo adjuvant settings, Anthracycline and taxanes based regimens; platinum agents, antimetabolites and antiangiogenic agents are showing promising results. During neoadjuvant chemotherapy, patients should be closely monitored for the evidence of progression. Chemotherapy regimens should be modified effectively if progression of the tumor is evidenced. [6].

Several studies reported platinum-based neoadjuvant chemotherapeutic regimens effective for TNBC. There is no standard chemotherapy regimen for TNBC. Available options include anthracyclines, taxanes, platinum and alkylating agents. Sun W and colleagues investigated TNBC patients treated with adjuvant chemotherapy consisting of 5-fluorouracil, epirubicin and cyclophosphamide (FEC). They observed lymph node status as a prognostic indicator of OS and DFS among these patients. [7] Cyclophosphamide, methotrexate and flurouracil (CMF) regimen was found to be superior to cyclophosphamide, epirubicin, flurouracil (CEF) regimen in terms of 5 year OS among TNBC patients in analysis from MAS study [8].

Among patients with early stage TNBC, Anthracycline/taxanes based chemotherapy is appropriate and prescribed commonly. For advanced stage TNBC, conventional management starts with the cytotoxic chemotherapy. Management of palliative cytotoxic regimen is somewhat similar to other molecular subtypes. Poly-chemotherapy is reserved for stage IV symptomatic or rapidly progressing visceral TNBC, while sequential single agents opted for asymptomatic advanced disease. [5] Administration of chemotherapy in early stage of the disease is very important because TNBC has high rate of recurrence, distant metastasis and rapid progression within 3 years [9].

Breast conserving therapy

Because of aggressiveness of the disease, aggressive surgical intervention is considered as suitable therapeutic option for TNBC. There is a controversy regarding appropriateness of the breast conserving therapy for TNBC because of its highly aggressive nature and lack of targeted therapy. Data with respect to the outcome of BCT among patients with TNBC is conflicting. Some researchers reported increased local and regional recurrence and distant metastasis leading to reduced OS compared to other subtypes among patients who underwent BCT. [10,11] While some investigators observed statistically not significant difference in the rates of local recurrence and period of DFS for patients treated with BCT for TNBC vs non-TNBC. Hence they concluded BCT as an appropriate therapy that should be offered routinely to TNBC patients. [12,13] Bhatti AB et al supported favorable role of BCT in TNBC, despite of young age at the time of diagnosis, strong family history and poorly differentiated tumor [9].

Radiotherapy

Radiation therapy is useful therapeutic modality in the management of TNBC. Radiation therapy of the chest wall and regional area after the surgery can be offered. It is routinely used in BCT. But because of heterogonous nature of TNBC, role of radiation therapy remained doubtful in some studies. Chief concern in administration of radiation therapy in TNBC is whether the tumor is radio resistant or not. Radio resistance nature of TNBC has been suggested due to certain biological features like ERp29 expression and over expression of HER1 or mir-27. After surgical intervention, radiation therapy is advised in high-risk patients, positive resection margins, presence of 1-3 positive axillary lymph nodes and T3-T4 tumors. [2] TNBC women with BRCA1 mutations and tumor lacking functional BRCA1 are deficient in double strand DNA break repair due to homologous recombination. In such cases TNBC is highly radiosensitive. Occult BRCA1-deficient tumor foci in breast and surrounding tissue can be eradicated by radiotherapy after conservative breast surgery and prevent locoregioanal relapse [14].

Metastasis

TNBC exhibit more aggressive clinical behavior, metastatic pattern and worse outcome. They tend to metastasize to lungs, liver and central nervous system. Also frequency of involvement of lymph nodes is high for small size of tumor. [15] Approximately 15% of TNBC patients tend to have secondaries in brain. [6] In comparison with other subtypes, survival after recurrence of TNBC is of short duration with limited options for the management, hence prognostic factor. Rate of regional recurrence is high among TNBC patients as compared to other subtypes. Hence, sentinel node biopsy and axillary resection should be preferred for good outcome. Currently there are no standards for TNBC chemotherapy in metastatic settings. One should consider age of the patient, comorbidities, and tumor burden and disease free interval.

Management of TNBC is specifically challenging one and complex as it lacks a targeted treatment approach. It implies multidisciplinary approach for improved survival including surgery, chemotherapy and radiotherapy. Role of BCT is controversial in the management of TNBC. But it must be accompanied by concomitant systemic chemotherapy. Patients with TNBC frequently present with tumors of higher grade, large size, advanced stage at younger age compared to other subtypes of breast cancer. Locoregioanal management is same as that of other types of invasive breast cancer. Mastectomy with or without adjuvant chemotherapy or breast conservation followed by adjuvant radiotherapy is routinely practiced modalities.

Conclusion

TNBC is a highly aggressive tumor diagnosed frequently in younger and premenopausal women. Because of absence of ER, PR and HER2, it does not respond to hormonal or trastuzumab therapies. There is no effective specific targeted therapy for TNBC. Clinical profile of TNBC differs from other subtypes; hence treatment strategy must be planned cautiously and effectively. In metastatic settings, the course of the disease is more aggressive resulting in worse prognosis. Researchers need to identify reliable predictive biomarkers of TNBC and new therapeutic agents against the known molecular pathways to improve the prognosis of the disease.

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