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Mini Review

Metastatic Breast Cancer: Mini Review

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Abstract

Metastatic Breast Cancer (MBC) is very devastating disease, not curable and associated with poor outcome. Rate and site of metastasis varies significantly, but it depends mainly on primary subtype of the tumor, age and stage of the disease. Metastasis of breast cancer is multistep process with complex mechanism. The crosstalk between disseminated tumor cell and microenvironment has been identified as critical determinant of metastasis. Most common target organs for breast cancer metastasis are bone, lungs, liver and brain along with distant lymph nodes. Bone metastasis is the most frequent metastatic site.

Early detection of metastatic lesions improves survival rate as well as quality of life of breast cancer patients. Most of the patients of MBC are treated with systemic therapy that include hormone therapy, chemotherapy, targeted therapy or combination of these to reduce the tumor burden, relieve the symptoms and improve survival. MBC patients should be focused for the palliation of the symptoms. Although chemotherapy remains the major treatment, MBC patients need additional supportive care like nutrition; psychology, nursing and palliative care services.

Keywords: Metastatic breast cancer; Chemotherapy; Bone

Introduction

Chief complication of breast cancer is the metastasis of malignant cells to surrounding tissues and distant organs. It remained the biggest hurdle for curing breast cancer. Around 90% of the patients die of metastasis when malignant cells spread systemically to distant vital organs. Such multiple lesions cannot be resected surgically and they are resistant to systemic therapy also leading to deterioration of health [1]. The risk of metastasis varies from person to person and depends on stage at the time of diagnosis, biological characteristics of tumor and the treatment received for primary breast cancer. Generally it is accepted that Metastatic Breast Cancer (MBC) is very devastating disease, not curable and associated with poor outcome. It can be an incidental finding in asymptomatic patients or may present with non-specific generalized symptoms like weight loss and malaise.

MBC is the leading cause of breast cancer-related death. Currently up to 5% of cases present with incurable metastasis at the time of initial diagnosis only and in addition approximately 10% to 15% of patients develop metastasis within 3 years of diagnosis [2]. Rate and site of metastasis varies significantly, but it depends mainly on primary subtype of the tumor, age and stage of the disease.

Despite of the availability of modern anticancer and endocrinal therapeutic drugs, surgical techniques and radiation therapy, 30% to 40% of breast cancer patients may suffer from distant relapse and succumb to the disease. One more limitation to opt suitable therapy for MBC is the lack of prognostic indicators that can predict which type of patients should receive more aggressive combination chemotherapy regimens for MBC [3]. Chemotherapy is the mainstay of treatment of MBC patients and with tremendous advanced progress in clinical oncology, synthesis of new anticancer drugs has led to the progress of management of MBC.

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Metastatic Breast Cancer

Metastasis of breast cancer is multistep process. Mechanism of development of metastasis is very complex. The crosstalk between disseminated tumor cell and microenvironment has been identified as critical determinant of metastasis [4]. Most common target organs for breast cancer metastasis are bone, lungs, liver and brain along with distant lymph nodes. Bone metastasis is the most predominant metastatic site. It has been reported that 40% to 75% cases of breast cancer include bone metastasis. Up to 13.6% of stage I to III breast cancer patients eventually develop bone metastasis at 15 years of follow-up [5]. The mechanism of bone metastasis is very complex. It occurs in asystematic sequence that involves different mutations, micro environmental cues, inflammatory response and other factors [6]. It begins with epithelial-to-mesenchymal transition of locally invasive malignant cells, which enter lumina of blood vessels by intravasation. In comparison to visceral metastasis, bone metastasis has better prognosis with median overall survival of 40 to 65 months [7].

Bone marrow is also site for secondaries by blood born disseminated breast cancer cells. Disseminated cancer cells express CXCR4 (chemokine receptor) through which they spread to in bone marrow as reservoir as well as to distant organs like liver, lungs [8]. Molecular assay techniques can detect even single disseminated tumor cell in bone marrow or peripheral blood at the frequency of 10. These cells are detected in around 10% to 60% of the patients before developing manifestations or histological signs of metastasis [9]. In ER+ subtype, bone is a major target to develop secondaries. Bone is also rich in estrogen to maintain bone homeostasis and remodeling. HER2+ tumors are driven by ERBB2/3 heterodimer that may cause brain metastasis because brain has few immune cells [1]. Among triple negative breast cancer patients, metastasis occurs within first 5 years after primary, hence prognosis is worst [10]. HER2+ tumors are also very aggressive and for extra cranial lesions effective therapies

are there, but brain metastasis remained a great challenge [11]. Breast cancer is the second commonest source for brain metastasis as 10% to 15% of MBC patients develop secondaries in brain [12].

Inspire of advances in diagnostic and therapeutic modalities, MBC remains the major cause of cancer related morbidity and mortality worldwide. Early detection of metastatic lesions improves survival rate as well as quality of life of breast cancer patients. So there is dire need of validated biomarkers to identify women at risk of metastasis after diagnosing primary disease. Mammography has limitations and unreliable for diagnosing metastasis with false positive rate of about 50% cases of MBC [13]. Sentinel lymph node biopsy is useful to detect regional metastasis but for distant metastasis it has to be used in combination with imaging techniques. Early detection of not only micro metastasis, but of early mutational events that are responsible for the drug resistance is needed. Measurement of circulating tumor DNA may be useful for this purpose. Micro RNAs (miRNAs) are emerging as promising biomarker for metastasis of breast cancer as it has been observed to link to all stages along the cascade of MBC [2].

Multimodality Therapy for MBC

Substantial advancements for treatment of primary localized breast cancer have improved survival of the patients. But MBC still lacks effective treatment and remains major cause of mortality. Most of the patients of MBC are treated with systemic therapy that include hormone therapy, chemotherapy, targeted therapy or combination of these to reduce the tumor burden, relieve the symptoms and improve survival. Still there is controversial debate regarding the use of combination chemotherapy or sequential single agent regimens for the management of MBC. Patients with extensive visceral metastasis get benefited from combination chemotherapy with rapid disease response. If disease is stabilized with combination chemotherapy, sequentially single agent regimens can be offered. Single agents' regimens can be used as salvage therapies. The most common chemotherapeutic agents used are anthracyclines (doxorubicin and epirubicin), taxanes (paclitaxel, docetaxel), Fluorouracil (5-FU) and cyclophosphamide. Management of MBC depends chiefly on molecular subtype of breast cancer. Triple negative breast cancer patients have very limited options.

MBC patients should be focused for the palliation of the symptoms. Patients with bone metastasis can be managed by offering bisphosphonates. Balancing the relief of symptoms, prolongation of survival and toxicity of therapy is very critical among MBC patients. Among patients who are at high risk to develop metastasis lesions from cross seeding, self-seeding, the lesion should be kept locally confined and administration of cytotoxic therapies can benefit re-seeding. Once metastasis is detected, it should be eradicated by novel therapies like immunotherapy, targeted therapies and prevent further dissemination and colonization of tumor cells in distant organs by blocking metastatic cascade and organ-specific tropism. Patients with bone-only metastatic breast cancer have better prognosis in comparison with other visceral sites metastasis [14].

Although chemotherapy remains the major treatment, MBC patients need additional supportive care like nutrition; psychology, nursing and palliative care services. Also there is need of exploration of accurate biomarkers, which can predict response to the chemotherapeutic agents among these patients with different molecular subtypes [15,16]. Outcome of MBC has been reported to be poor, but some researchers' 1% to 2% cases with long-term (more than 10 years) disease free survival rate with modern adjuvant combination chemotherapy. Patients of young age with low volume of the disease (oligometastatic) are long-term survivors [16].

Conclusion

Metastatic pattern of breast cancer patients depend on demographic, clinical, pathological and genetic factors. It also has profound effect of adjuvant therapy received for the primary lesions. Identification of risk factors related to MBC is of paramount importance. It can be used as a prediction tool and detect high-risk individuals to use specific targeted agents among them for improved survival.

Management of MBC is challenging because of lack of optimal single strategy for all patients. With tremendous advances in the field of pharmacology, new biologic and targeted drugs are available for MBC patients. But use of such expensive drugs among MBC patients remains a critical issue. These patients should be focused for the palliation of symptoms to improve quality of life.

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