COMMENTARY

Anticancer Therapy for Breast Cancer Patients with Skin Metastases Refractory to Conventional Treatments

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Abstract

Skin metastases of breast cancer are usually late events in the course of tumor progression and signify a poor prognosis. They may remain as a therapeutic challenge especially after failure of standard treatments. Topical interventions, together with or without radiotherapy, may only palliate the symptoms temporarily. However, there may be alternative treatment modalities for unresectable breast cancer skin metastases resistant to chemotherapy and radiotherapy. There are various genetic alterations in tumors and therapeutic potential of expression patterns for factors like epidermal growth factor receptor may have important clinical implications in case of disease refractory to the conventional treatments. Here, we clarified the therapeutic options and genetic alterations in skin metastatic breast cancer patients refractory to standard chemotherapeutics.

Keywords: Anticancer therapy - breast cancer - skin metastases - refractory

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Introduction

In women, skin metastases are seen more commonly in breast cancer than in any other malignancy. The presence of skin metastases signifies disseminated disease and a poor prognosis. For this reason, aim of the treatment is usually to delay disease progression, control symptoms, and maintain quality of life. However, breast cancer is a genetically heterogeneous disease. Even after refractory to conventional treatments, there might be subgroups of breast cancer patients with cutaneous metastases who could already response to certain anticancer therapies.

Effective Chemotherapeutics in Refractory Patients

After progression on standard chemotherapy regimens, few treatments have shown to be effective for regression of the skin metastases from breast cancer. In fact, the increasing use of anthracycline and taxane-based chemotherapies in the neoadjuvant and/or adjuvant settings has led to investigate new cytotoxic therapies. The primary tumor and metastasis of skin and lymph nodes showed a significantly better response to capecitabine treatment than other metastases such as lung, liver and bone (Tsuyuki, 2010). This could be explained by the high penetration capacity of capecitabine and its metabolites to malignant and healthy tissue (Mader et al., 2003). In two patients who received capecitabine showed a dramatic response with resolution of their skin lesions (Sideras, 2008). In another two published case reports of breast cancer patients, oral agent S-1 showed its efficacy for the skin metastases developed or progressed after major chemotherapy combinations (Tokugawa, 2009; Hirao et al., 2011). So, current data potentially encourage documentation of cutaneous specific responses from fluorouracil (5-FU) derivatives in breast cancer patients with multiple skin metastases. Cisplatin either in combination with 5-FU or alone was active in breast cancer patients with skin metastases refractory to both anthracyclines and taxanes because of the observation of remarkable objective responses more frequently in skin metastatic cases (Coşkun, 2011). Intratumoral administration of cisplatin is also effective in the local treatment of cutaneous tumor lesions of breast cancer (Rebersek, 2004). In addition, Franchina et al. reported two cases of disseminated TN breast cancer with extensive cutaneous metastases and a favorable response to pegylated liposomal doxorubicin in combination with gemcitabine (Franchina et al., 2012).

Efficiency of Anti-EGFR Agents

Breast cancer subtypes based on the hormonal receptor (HR) and human epidermal growth factor receptor 2 (HER2) status may reflect skin changes and soft tissue infiltration patterns at the time of skin metastasis. The presence of skin ulceration was shown predominantly in the HR+ group than in the others and erythematous infiltrations were more commonly found in the triple-negative (TN) group (Kong et al., 2011). On CT scans, soft tissue infiltration appeared to be more common in the HER2-enriched and TN groups than in the HR+ group and

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erythematous infiltrative lesions were more commonly established in patients with epidermal growth factor receptor (EGFR) overexpression (Kong et al., 2011). EGFR, a transmembrane receptor tyrosine kinase of the erbB family, is expressed in 15-30% of all breast cancers. Since squamous cell carcinoma (SCC) has been shown to express the EGFR, there is an increasing evidence of cetuximab efficacy in non-melanoma skin cancers. In a phase II trial, the total response rate of cetuximab is almost 50% in patients with SCC (Wollina, 2012). Gholam et al reported that; combination of cetuximab with paclitaxel established a major reduction in the skin metastases of a heavily pretreated patient with EGFR-positive, TN breast cancer (Gholam, 2007). Therefore, EGFR inhibitor cetuximab could be an option for skin metastases of breast cancer patients with EGFR overexpression.

Molecular Approaches

Breast tumors with early skin metastases expressed E-cadherin infrequently (Sihto et al., 2011). It was also shown that activating ras mutations and allelic loss of the c-met proto-oncogene are never involved in either the initiation or metastasis to skin in human breast cancer (Rochlitz et al., 1989; Ng et al., 1997). Besides, breast cancer patients with skin metastases and cutaneous local recurrences may exhibit different growth patterns due to different degrees of angiogenesis (Colpaert et al., 2003). Vascular endothelial growth factor (VEGF-D) expression was detected only in the inflammatory subtype of breast cancer and in tumors which developed an inflammatory skin metastasis (Kurebayashi et al., 1999). So, there could be a possible relationship between the expression level of VEGF and the development of skin metastasis. The recognition of different degrees of hypoxia-driven angiogenesis in cutaneous breast cancer deposits may have important implications for the utilization of anti-angiogenic therapies. Meanwhile, Bevacizumab which is a VEGF-A inhibitor, was found to be harmful in selected breast cancer patients with metastatic cutaneous involvement (Cottu, 2011). This deleterious side effect of bevacizumab in patients with skin metastases could possibly be related with the wound healing impairments of this drug.

Protein expression pattern of the primary breast carcinoma may influence the distant metastatic site. In order to understand the underlying mechanisms of organ-specific metastases, several gene and protein expression signatures have been identified in the primary tumor. These expression markers often include various genes coding for adhesion molecules, such as activated leukocyte cell adhesion molecule which demonstrated more significant protein expression in breast cancer skin metastases compared with other metastatic sites (Ihnen et al., 2011). Circulation of the leukocytes share many similarities with tumor cell migration and metastasis, which is critically regulated by chemokines and their receptors. Expression of chemokine receptors in the primary tumor predicts the site of metastatic relapse in patients with axillary lymph node positive breast cancer (Andre et al., 2006). If confirmed, these findings could have important clinical implications regarding the treatment and follow-up of patients with primary breast cancer.

Conclusions

The discomfort of skin metastases increases as the tumor spreads and more tissue destruction occurs. Topical interventions are attractive for its easy self-administration without any major systemic interference. Combination cryosurgery with hyperthermia, radiation therapy and its modalities, topically applied miltefosine or imiquimod and radiobiological approaches like re-irradiation in conjunction with liposomal doxorubicin showed only modest activities in a relatively heavily pretreated patient population, but they are very effective in order to palliate the symptoms (Fritz 2000; Smorenburg, 2000; Kouloulias 2003; Adams, 2012; Hachisuka, 2012). However, all these treatments are not long-term solutions and more efficient medications are necessary. Thus, it is essential to define specific genetic alterations of the tumor cells which increase their metastatic potential. Owing to their therapeutic opportunity, organ specific targets could yield to more effective treatments which may enhance the activity of chemotherapies and improve the prognosis of metastatic breast cancer patients.

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