EGFR in Inflammatory Breast Cancer

Subjects: Oncology

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Epidermal growth factor receptor (EGFR), also called ErbB1 or HER1, belongs to ErbB family of receptors, which also includes HER2, HER3, and HER4. Inflammatory breast cancer (IBC) is the most lethal and aggressive form of breast cancer; it is highly likely to spread to other sites in the body.

Keywords: inflammatory breast cancer ; signaling pathways ; tumor microenvironment

1. Biological Functions of EGFR Pathway in IBC

Upon binding to its ligands, EGFR forms an active homodimer or heterodimerizes with other ErbB family members such as HER2, activating downstream pathways involved in cell growth, proliferation, migration, and differentiation such as the mitogen-activated protein kinase (MAPK), AKT, c-Jun N-terminal kinase (JNK), and phosphoinositide phospholipase C/protein kinase C (PLC/PKC) signaling pathways. EGFR is overexpressed in IBC and other types of breast cancer [1][2]. EGFR expression independently predicts a high recurrence rate and shorter survival duration in patients with IBC. The 5-year overall survival rate of IBC patients with EGFR-positive disease is significantly lower than that of patients with EGFR-negative disease [1].

EGFR signaling regulates tumor growth through its downstream AKT and ERK pathways. EGF and AREG ligands can activate EGFR signaling and promote the proliferation of IBC SUM149 cells in vitro [3]. In contrast, inactivation of the EGFR pathway using tyrosine kinase inhibitors gefitinib and erlotinib or EGFR knockdown suppressed the proliferation of IBC cells through the MAPK/ERK pathway as well as tumor growth in vivo [4][5]. Patients with IBC have a high tendency of distant metastasis. Erlotinib treatment reduces the invasion of IBC cells, reduces the expression of epithelial-to-mesenchymal transition (EMT) markers, and inhibits spontaneous lung metastasis in vivo [5].

Patients with IBC have inflammatory clinical characteristics such as diffuse erythema and edema of the breast, and COX-2 is an important inflammatory molecule in IBC. Wang et al. [6] demonstrated that the expression of EGFR and COX-2 correlate with each other in IBC tumor biopsy samples and that EGFR regulates COX-2 expression in IBC cells.

IBC patients have high expression of aldehyde dehydrogenase 1 (ALDH1), a CSC marker, which correlates with metastasis and worse patient outcome [7]. It has been reported that the EGFR pathway regulates CSC in IBC, as indicated by the reduced formation of primary and secondary mammospheres, and reduces CD44+/CD24− and ALDH+ populations—a hallmark of breast CSC—in IBC cells by the depletion of EGFR or inhibition of EGFR signaling [6]. The regulation of CSC by EGFR is mediated by COX-2 and nodal signaling in IBC.

The EGFR pathway regulates the crosstalk between tumor cells and TME. Lacerda et al. [8] showed that the co-injection of MSCs with IBC SUM149 cells significantly increased skin invasion and metastasis in vivo, which are the clinical features of IBC. They also found a higher expression of phosphorylated EGFR (pEGFR) and more metastasis in tumors produced by the co-injection of SUM149 with mesenchymal stem cells compared with tumors grown from SUM149 cells only; the EGFR inhibitor erlotinib abrogated these effects [9]. In addition, the researchers showed that pEGFR expression in the stroma correlates with its expression in tumor cells in IBC patients but not in non-IBC patients [9]. TAMs are another main member of the TME and contribute to tumor progression and invasion by inducing immunosuppression, mediating tumor matrix remodeling, and supporting vascular potency [10][11][12]. Invasive tumor cells can migrate together with macrophages in primary mammary tumors in response to EGF and colony-stimulating factor 1 (CSF-1), which can be blocked by inhibiting either EGFR or CSF-1 signaling [13]. Macrophages also help tumor cells enter blood vessels; however, the inactivation of EGFR signaling blocks this process [14]. Treatment of human THP1 monocytes with erlotinib inhibited the polarization of M2 macrophages from monocytes (N.T. Ueno, unpublished data).

2. Targeting EGFR Pathway in IBC

Clinical trials of EGFR-targeted therapy for breast cancer patients have not shown clear clinical benefits.

Erlotinib binds to the intracellular domains of EGFR and inhibits kinase activity and downstream signaling. In vitro studies indicated that erlotinib treatment inhibited IBC cell proliferation, anchorage-independent growth, cell motility, the COX-2 inflammatory pathway, and CSC marker-bearing cells in IBC [5][6]. In vivo, erlotinib reduced the growth of IBC primary tumors and metastasis to the lung [5].

Panitumumab is a humanized anti-EGFR monoclonal antibody. It binds to EGFR and blocks the binding of EGF ligand, thus inactivating EGFR signaling. There have been two clinical studies of panitumumab in combination with neoadjuvant chemotherapy in patients with IBC (ClinicalTrials.gov Identifier: NCT01036087 and NCT02876107; **Table 1**). NCT01036087 (Phase II Study of Panitumumab, Nab-paclitaxel, and Carboplatin for Patients With Primary Inflammatory Breast Cancer (IBC) Without HER2 Overexpression) is a single-arm phase 2 study of neoadjuvant therapy with panitumumab, nab-paclitaxel, and carboplatin (PNC) followed by 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) in patients with newly diagnosed, HER2− primary IBC [15]. Patients received one dose of panitumumab followed by four cycles of PNC weekly and then four cycles of FEC every 3 weeks. The pCR rate was 28% in all evaluable patients, 42% in TN-IBC patients, and 14% in HR+/HER2− IBC patients. The treatment regimen had acceptable hematological and dermatological toxic effects, and there were no treatment-related deaths. A correlative study identified that pEGFR and COX-2 expression at baseline correlates with pCR. This trial indicates that panitumumab may enhance the response of IBC patients to neoadjuvant chemotherapy.

Table 1. Clinical trials in inflammatory breast cancer.

Drug Studied	Target(s)	Combined Agents	Type of Study	Patient Population	Trial Identification No.
Panitumumab	EGFR	Carboplatin, nab-paclitaxel, 5-fluorouracil, epirubicin, and cyclophosphamide	Phase 2, single-arm	Primary HER2− newly diagnosed IBC	NCT01036087
Panitumumab	EGFR	Carboplatin, nab-paclitaxel, 5-fluorouracil, epirubicin, and cyclophosphamide	Phase 2, randomized	TN-IBC	NCT02876107
Neratinib	EGFR, HER2, and HER4	Neratinib, pertuzumab, and trastuzumab with paclitaxel	Phase 2	HER2+ IBC; HR+/HER2− IBC	NCT03101748
Trastuzumab	HER2	Trastuzumab, doxorubicin, paclitaxel, cyclophosphamide, methotrexate, 5-fluorouracil, and tamoxifen	Phase 3	Newly diagnosed HER2+ locally advanced breast cancer or IBC	ISRCTN86043495
Pertuzumab and trastuzumab	HER2	Pertuzumab, trastuzumab, and docetaxel	Phase 2	Locally advanced, inflammatory or early stage HER2+ breast cancer	NCT00545688
Lapatinib	HER2	Lapatinib	Phase 2	HER2+ IBC	NCT00105950
Lapatinib	HER2	Lapatinib and paclitaxel	Phase 2	Newly diagnosed IBC	EGF102580
Lapatinib	HER2	Lapatinib, entinostat, with or without trastuzumab	Phase 1b	HER2+ breast cancer	NCT01434303
Ruxolitinib	JAK1/2	Ruxolitinib with preoperative chemotherapy	Phase 1/2	TN-IBC	NCT02041429
Ruxolitinib	JAK1/2	Ruxolitinib, paclitaxel, doxorubicin, and cyclophosphamide	Phase 2, randomized	TN-IBC	NCT02876302
Bevacizumab	VEGF	Bevacizumab, doxorubicin, and docetaxel	Interventional	Inflammatory and locally advanced breast cancer	NCT00717405
Bevacizumab	VEGF	Bevacizumab, fluorouracil, epirubicin, cyclophosphamide, and docetaxel	Phase 2	Non-metastatic HER2− IBC	NCT00820547

Drug Studied	Target(s)	Combined Agents	Type of Study	Patient Population	Trial Identification No.
Rebastinib	**Tie2**	**Rebastinib and paclitaxel**	**Phase 1b/2**	**Advanced or metastatic solid tumors including IBC**	**NCT03601897**

Abbreviations: IBC, inflammatory breast cancer; nab, nanoparticle albumin-bound; TN-IBC, triple-negative inflammatory breast cancer.

The definitive role of EGFR-targeted therapy will be further determined by an ongoing randomized phase 2 study of carboplatin and paclitaxel with and without panitumumab in TN-IBC patients (ClinicalTrials.gov Identifier: NCT02876107; A Randomized Phase II Study of Neoadjuvant Carboplatin/Paclitaxel (CT) Versus Panitumumab/Carboplatin/Paclitaxel (PaCT) Followed by Anthracycline-Containing Regimen for Newly Diagnosed Primary Triple-Negative Inflammatory Breast Cancer.) [16]. This trial plans to recruit 72 patients and randomize them into two arms. In Arm A, patients receive panitumumab as a single agent in the window period followed by weekly panitumumab and paclitaxel and triweekly carboplatin for a total of four cycles. Patients in Arm B receive the same regimen as those in Arm A but without panitumumab. In both arms, this treatment will be followed by treatment with doxorubicin and cyclophosphamide for 4 cycles and then surgery. The pCR, disease-free survival, and overall survival (OS) rates, as well as the safety and tolerability of treatment regimens, will be determined.

Neratinib is a pan-EGFR receptor tyrosine kinase inhibitor that interacts with the catalytic domain of EGFR, HER2, and HER4. A phase II study of neratinib, pertuzumab, and trastuzumab with paclitaxel followed by doxorubicin and cyclophosphamide in HER2+ primary IBC, and neratinib with paclitaxel followed by doxorubicin and cyclophosphamide in HR+/HER2− primary IBC is ongoing (ClinicalTrials.gov Identifier: NCT03101748; **Table 1**) [17]. This study will determine the efficacy of neratinib with paclitaxel and with or without pertuzumab and trastuzumab in IBC and metastatic breast cancer.

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