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Nanocarrier(s) as an Emerging Platform for Breast Cancer Therapy

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ABSTRACT

Nanocarrier(s) are the potential carrier to revolutionize breast cancer diagnosis and therapy. Development of nanocarrier(s) loaded with drug, which is targeted to the cancer cell using ligand mediated drug delivery system. Some therapeutic nanocarrier(s) have been approved for clinical use. There are only limited numbers of clinically approved nanocarriers that incorporate molecules to selectively bind and target cancer cells. Targeted drug delivery system is a unique approach for drug delivery to the appropriate site which is highly efficient, biocompatible, and non-immunogenic. The receptor mediated endocytosis is one of the targeting approaches specially for targeting anticancer drug to cancerous site. Breast cancer cells have overexpressed receptors like folate, transferrin, estrogen, human epidermal growth factor receptors (HER) which can be used for effective site specific drug delivery to cancerous cells using appropriate receptor specific ligand. This review examines some of the nanocarrier and discusses the challenges in translating basic research to the clinic and the potential predictive markers of resistance to HER2-targeted therapies in breast cancer, novel drugs and drug combinations, including the promise of immunotherapy.

Keywords: Breast cancer, Nanocarrier, Tumor, Receptor, Nanotechnology, immunotherapy.

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INTRODUCTION

Cancer nanotechnology offers many opportunities in diagnosing and treating cancers due to their many possible and interesting interactions (Parodi et al., 2012, Tay et al., 2016, Shi et al., 2011, Molinaro et al., 2011, Matsumoto et al., 2016). Several nanoparticles (NPs) could induce endothelial leakiness (NanoEL)(Setyawati et al., 2013, Setyawati et al., 2017, Tay et al., 2017, Wang et al., 2018, Qiu et al., 2017), cancer nanomedicines, considered to destroy the tumour cel (Ding et al., 2019, Li et al., 2018, Peng et al., 2018), may also unintentionally induce leakiness of the tumour vasculature, thereby lowering the barrier for intravasational entry of surviving cancer cells into the circulation. The growing evidence of nanomaterial can cause endothelial gaps that could be tens to hundreds of micrometres in width and large enough for whole cells to traverse (Setyawati et al., 2013, Setyawati et al., 2017, Setyawati et al., 2016), it is imperative then to establish whether cancer metastasis may be appreciably enhanced by nanomaterials. Moreover, these NPs have wide population exposure through processed healthcare products and vaccines (Yamashita et al., 2011, DeLoid et al., 2014, Hirai et al., 2016). This high population penetration may form an elevated basal level of NPs in cancer patients, thus extending the biological effects to situations where nanomedicine is not involved. In addition, there were possibly new sites of metastasis, suggesting that NPs or cancer nanomedicines may promote cellular entry to tissue sites previously inaccessible to the metastatic cells. The combination of these cellular events together with in vivo evidence will provide insights into how NPs could unintentionally promote cancer metastasis in a time- and concentration-dependent manner. The more intersecting approach starts with the discovery of the human epidermal growth factor receptor 2 (HER2) (King et al, 1985; Schechter et al, 1985), its association with poor prognosis in breast cancer (Slamon et al, 1987) and the potential of recombinant DNA technology to produce monoclonal antibodies developed as a promising strategies in the treatment of breast cancer. Monoclonal antibody trastuzumab (herceptin, Genentech, South San Francisco, CA, USA) used in oncology from non-specific chemotherapy to a molecularly targeted approach (Esteva, 2004). Trastuzumab binds domain IV of the extracellular component of the HER2 protein located close to the cell membrane, resulting in signal transduction blockade and prevention of HER2 cleavage. Addition of trastuzumab to conventional cytotoxic chemotherapy improved overall response rates (ORR), time to progression (TTP) and overall survival (OS) rates (Slamon et al, 2001).

Lapatinib, a tyrosine kinase inhibitor of EGFR and HER2 was found to be effective in combination with capecitabine in patients whose metastatic tumours were progressing on trastuzumab-based chemotherapy (Geyer et al, 2006). Pertuzumab (Perjeta, Genentech) is a humanised monoclonal antibody directed against domain II of the extracellular component of HER2, which is where receptor dimerisation occurs (Adams et al, 2006). Antibody–drug conjugates are another approach in oncology drug development. Ado-trastuzumab-DM1 (T-DM1, Kadcyla) combines the HER2-targeted antitumor properties of trastuzumab with the antimicrotubule agent DM1 allowing preferential intracellular drug delivery to the HER2+ tumour cells. Trastuzumab, pertuzumab and T-DM1 can all induce antibody-dependent cellular cytotoxicity. Thus, HER2 remains to be the most important predictive factor of response to HER2-targeted therapies (Seidman et al, 2001). The HER2+ breast cancer means if the ratio of HER2/cep17 is at least 2.0 or if the HER2 gene copy number is 46 (Wolff et al, 2013). Despite improvements in progression-free survival (PFS) and OS rates, HER2+ MBC remains an incurable disease and clinical research remains as important as ever. In this article we discuss the optimal sequencing of HER2-targeted therapies in HER2+ MBC based on line of therapy. We discuss potential predictive markers of resistance to HER2-targeted therapies and review ongoing efforts to incorporate novel drugs and drug combinations, including the promise of immunotherapy.

MOLECULAR MECHANISM OF RESISTANCE AND ONGOING CLINICAL TRIALS

The quantitative expression of human epidermal growth factor receptor 2 (HER-2), either in terms of protein or mRNA levels within the clinically-defined HER2-positive tumours seems to predict higher or lower probability of response, as shown repeatedly from pre-specified analyses of very influential prospective trials for examples; CLEOPATRA, EMILIA, NEO-SPHERE, NEO-ALTTO and TRYPHAENA) (Baselga et al, 2012; Gianni et al, 2012; Schneeweiss et al, 2013; Verma et al, 2012). Hyperactivation of the PI3K pathway by activating mutations or loss of PTEN expression has been associated with resistance to trastuzumab-based chemotherapy (Esteva et al, 2010; Nagata et al, 2004). Several studies shows that the PTEN loss may be a marker of trastuzumab resistance, patients who had been previously treated with trastuzumab and subsequently developed metastatic breast cancer, the metastatic tumours expressed lower levels of PTEN compared with primary tumours (Chandarlapaty et al, 2012). Though, PTEN expression in primary breast cancer was not predictive of disease-free survival (DFS) or OS in adjuvant trastuzumab trials. Other proposed markers of trastuzumab resistance include a truncated form of HER2 (p95), PIK3CA mutations (Berns et al, 2007; Esteva et al, 2010), HER2/IGF-IR dimerisation (Nahta et al, 2005) and Src activation (Zhang et al, 2011). Molecular approaches provide target for rational drug development, still none of these markers have been validated in prospective clinical trials to exclude patients from HER2-directed therapies.

NOVEL APPROACHES FOR THE TREATMENT OF BREAST CANCER

1. Tyrosine Kinase Inhibitors

Tyrosin kinase inhibitors used in breast cancer therapy. Afatinib is an orally active irreversible dual inhibitor of EGFR and HER2 receptors. In a phase II study, afatinib monotherapy in heavily pretreated HER2+ MBC demonstrated partial response (PR) in 4 patients (10% of 41) and stable disease in 11 patients (37%of 41) (Lin et al, 2012). Neratinib is an orally active irreversible inhibitor of EGFR, HER2 and HER4 receptors. In a phase II open-label clinical trial, 240 mg of oral neratinib was administered to trastuzumab pretreated (n=66) and a trastuzumab naı¨ve cohort (n=70). The ORR was 24% and 56%, respectively, and the most common grade 3 toxicity was diarrhoea.

2. PI3K/Akt/mTOR Pathway Inhibitors

In preclinical studies, the synergistic effect of mTOR inhibitor inhibitors with trastuzumab and have shown to cause complete regression of mouse HER2+ mammary tumours (Lu et al, 2007) In a phase I/II trial of trastuzumab combined with mTOR inhibitor everolimus for HER2+ MBC, PR was seen in 15% patients and s.d.46 months in 19% (Morrow et al, 2011). BOLERO-3 was a phase III trial comparing vinorelbine and trastuzumab alone or in combination with everolimus in 569 patents with HER2+ MBC resistant to trastuzumab. The preliminary findings of this study show significant prolongation in TTP (5.8 months vs 7 months, HR: 0.78; 95% CI: 0.65–0.95; Po0.01) in the everolimus arm. Exploratory analysis of biomarkers in the BOLERO-3 trial suggests that the addition of everolimus to trastuzumab plus vinorelbine for HER2-positive advanced breast cancer may be most beneficial in patients with low PTEN or high pS6 levels (Jerusalem et al, 2013). No clear benefit of everolimus was observed in patients with normal PTEN or low pS6 levels. These data support the hypothesis that low PTEN expression is a marker of trastuzumab resistance (Nagata et al, 2004; Esteva et al, 2010). Subset analyses showed a larger benefit for the everolimus group in HER2+/HR_ tumours, compared with HER2+/HR+ tumours. This seems counterintuitive in view of the results of everolimus and exemestane in HR+ tumours (BOLERO-2. No treatment–biomarker interaction was reported between everolimus and PI3K mutations. Data from the Cancer Genome Atlas (TCGA-Network, 2012) suggest that despite a similar incidence of PI3K mutation in HER2 enriched and luminal tumours, markers of pathway activations were differently expressed in these two subtypes in the presence of PI3K mutations. Several PI3 kinase inhibitors are under phase 1/2 stage of development.

3. Heat Shock Protein 90 (HSP90) Inhibitor

HSP90 inhibitors cause the proteosomal degradation of oncoproteins such as HER2. Additionally, p-95HER2, which is a truncated form of HER2 and also a major mechanism of trastuzumab resistance, has been shown to undergo degradation by HSP90 inhibitors. Tanespimycin has been evaluated in HER2+ MBC that had previously progressed trastuzumab in the phase II setting. The ORR was 22%, the clinical benefit rate (ORR and SD for at least 6 months) was 59% and median PFS was 6 months (95% CI: 4–9 months). Another HSP90 inhibitor, ganetespib (STA- 9090), was tested as monotherapy in a phase II setting (Jhaveri et al, 2014). Using Simon stage design, in the first stage of this design, the study did not meet the primary endpoint of ORR. Modest activity was noted in heavily pretreated, trastuzumab-refractory patients. Based on the preclinical data that shows synergistic activity for combining HSP90 inhibitors with taxanes.

4. Other Targeted Strategies

The processes of tumor cell growth, angiogenesis and metastases associated with the KD019 is a small molecule that simultaneously blocks the tyrosine kinase of EGFR, HER2, Src and the vascular endothelial growth factor receptor 2 (VEGFR2). A phase I study of KD019 plus trastuzumab in HER2 overexpressed or amplified MBC is

ongoing for patients who have received two or more prior anti-HER2-directed therapies (Jhaveri et al (2014), Perlmutter Cancer Center at NYU Langone). It has been demonstrated that cross-talk between IGF-1R and HER2 as well as IGF mediated phosphorylation of HER2 results in trastuzumab resistance (Nahta et al, 2005, 2006), providing merit to exploring IGF-1R inhibitors such as Cixotumumab in clinical trials. Preclinical studies have shown upregulation of VEGF in HER2 overexpressed breast cancers, and the phase 2 study of trastuzumab and bevacizumab combination in HER2+ MBC was promising. However, bevacizumab, a monoclonal antibody against VEGF-A receptor, failed to improve PFS when combined with trastuzumab and docetaxel in a phase 3 trial compared with the non-bevacizumab arm (Gianni et al, 2013). One of the mechanisms of action of trastuzumab is thought to be induction of ADCC. It has been demonstrated that higher percentage of tumour infiltrating lymphocytes is associated with better response to trastuzumab in both adjuvant (Loi et al, 2013) and neoadjuvant setting. In correlative preclinical studies, higher PD-1 (programmed death-1), a T-cell checkpoint ligand expression, was associated with greater trastuzumab benefit. The negative regulator of T-cell mediated immune response is PD-1, so antibodies blocking PD-1 and its ligand PD-L1 enhance the T-cell mediated immune response. Trastuzumab may modulate tumour microenvironment by inhibiting tumour-mediated immunosuppression via factors like PD-1 (Stagg et al, 2011). Combining trastuzumab with anti-PD-1 and anti-PD-L1 antibodies showed greater tumour regression in mouse models of HER2+ mammary tumours. Therefore, there seems to be merit in exploring the impact of combining trastuzumab with inhibitors of negative T-cell regulation, such as anti-CTLA4 antibody, anti-PD-1 or anti-PDL-1, in HER2+ MBC. One peptide-based vaccine that merits special mention is the E75 vaccine derived from the extracellular domain of HER2 receptor. When compared with the unvaccinated arm, E75 was found to decrease recurrence rates when administered in the adjuvant setting for node positive HER2+ breast cancer (DFS rates at 22 months: 85.7% vs 59.8%) (Peoples et al, 2005).

CONCLUSIONS

Targeted drug delivery system is an inherent technique for the delivery of drugs to the appropriate sites for effective treatment. Apart from these, it also includes various ligand mediated drugs targeting with the help of varieties of nanocarriers which increase the therapeutic effect on target site with less side effects. The quantitative expression of human epidermal growth factor receptor 2 (HER-2), either in terms of protein or mRNA levels within the clinically-defined HER2-positive tumor. Lack of thoroughly validated predictive biomarkers has been one of the major hurdles to stratify breast cancer patients and to monitor tumor progression and response to the therapy. Investigations in clinic and preclinical models have provided some molecular and cellular mechanisms for the above challenges.

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