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A pan-HER-targeted approach for recurrent or late-stage cervical cancer therapy: mechanisms, recent advances, and clinical prospects

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Abstract. – OBJECTIVE: Over-expression of the epidermal growth factor receptor (EGFR) protein, along with gene amplification, is closely associated with recurrent cervical cancer and the disease's advanced stages. Additionally, it can have a direct impact on the disease's prognosis. The following are the members of the HER family: (i) EGFR/HER1; (ii) HER2; (iii) HER3; and (iv) HER4. Figure 1 shows its signalling pathway. The synergy between the members facilitates immune escape by tumour cells, which can lead to tolerance to HER inhibitors. A broad HER inhibitor, a pan-HER inhibitor, can irreversibly inhibit a cell membrane's HER receptors to their ligands, thereby blocking downstream signal-transduction cascades, inhibiting tumour growth, adhesion, invasion, differentiation, and metastasis. As such, pan-HER inhibitors may be an area of interest in treating recurrent or late-stage cervical cancer.

MATERIALS AND METHODS: Through a review of HER-family receptors and their molecular mechanism, we can conclude that pan-HER inhibitors do indeed have a positive impact on therapy for recurrent or late-stage cervical cancer patients.

RESULTS: This paper reviews the molecular mechanism that underlies receptors within the HER family, current developments in HER inhibitors, and the potential clinical impacts of pan-HER inhibitors in treating recurrent or late-stage cervical cancer.

CONCLUSIONS: Pan-HER inhibitors have been shown to improve prognoses for recurrent or late-stage cervical cancer patients. Pre-clinical studies show promising results, as well as the potential to improve results for recurrent or late-stage cervical cancer patients. Pan-HER inhibitors have also shown synergistic results in clinical and pre-clinical settings when combined with chemotherapy. However, long-term study is required regarding the combination of pan-HER inhibitors with radiotherapy and other targeted inhibitors. The question of whether or not these inhibitors have a more potent effect across the blood-brain barrier when compared to single HER-targeting agents may be an area of interest for future research. This idea will be explored in clinical cervical cancer trials.

Key Words:
EGFR, HER-family, Pan-HER inhibitors.

Introduction

As a gynaecological disease marked by a malignant tumour, cervical cancer is the second most prevalent condition of this kind[1]. Following a significant increase in recent years in the incidence of recurrent cervical cancer and the disease's advanced stages, a decrease has been observed in the average age of cervical cancer patients. Basic treatment for cervical cancer consists of surgery, chemotherapy, and radiation therapy[2]. However, the body's response to treatment is often less than satisfactory, and tumours often develop resistance in recurrent cervical cancer and during the disease's advanced stages[3]. In recent years, many efforts have been made to develop new strategies to treat these appearances of the disease[4,5]. In medical therapy, a range of molecular therapies are involved. Targeted molecular therapy has demonstrated the potential to reduce mortality rates associated with cervical cancer, and, simultaneously, to reduce the side effects of therapy affecting the organs. There are four main targeted therapeutic drugs[6]: monoclonal antibod-

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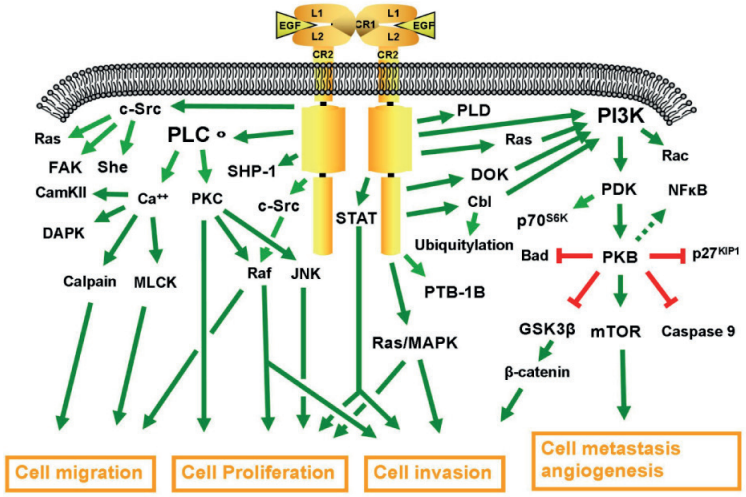

Figure 1. EGFR and EGF-like growth factor signalling pathways. The following pathways are activated when EGF or EGF-like growth factor ligands bind with HER1/EGFR: MAKP, PI3K/AKT, and JAK/STAT. Malignancy development, the proliferation of tumour cells, metastasis, and angiogenesis are promoted by the pathways. In terms of the abbreviations used throughout the figure, the reader should note extracellular signal-regulated kinase (ERK), mammalian target of rapamycin (mTOR), phosphatase and tensin homolog deleted from chromosome 10 (PI3K), signal transducer and activator of transcription (STAT), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), janus family kinase (JAK), and mitogen-activated protein kinase (MAPK).

ies derived from humans (mAb), small molecular inhibitors, small interrupting RNA (siRNA), and decoy receptors. Amongst these drugs, small molecular inhibitors work to inhibit molecular receptors by blocking kinase activation. Tyrosine kinases (TKs) can act as a catalyst for the transfer of phosphate groups from ATP to downstream tyrosine residues, changing protein activity, and thereby affecting other biological processes[7].

Among molecular inhibitors, the human epidermal growth factor (HER)[8] signalling pathway is critical in cancer progression. Epidermal growth factor receptor (EGFR) is frequently highly expressed in cervical cancer patients, as is the prototype member of the HER family, transmembrane receptors. It performs an important function in recurrence and progression of the advanced stages of the disease[3]. As such, the therapeutic strategies that are currently most commonly used are based on EGFR inhibition[9]. However, clinical improvements cannot be made without first ensuring that resistances to HER inhibition therapy are not built up. Currently, novel HER inhibitors have been demonstrated to more efficiently limit tumour resistance to EGFR inhibition. This is especially true for wide irreversible HER inhibitors, which is where pan-HER inhibitors are useful. Pan-HER inhibitors inhibit two or four HER-family receptors (known as dual- and pan-HER inhibitors, respectively). They can take the form of either tyrosine kinase inhibitors (TKIs) or a combination of antibodies responsible for targeting epitopes on EGFR, HER3, and HER2 that do not overlap. In the review, a summary was offered of the HER-family receptors' molecular mechanisms, together with recent developments regarding their use, and their future clinical prospects.

Materials and Methods

HER Ligands and Their Receptors

The following configuration-related receptors for tyrosine kinase are members of the HER family: (i) EGFR/HER1; (ii) HER2; (iii) HER3; and (iv) HER4[8] (Figure 1). As mentioned above, the over-expression of EGFR has been demonstrated to be strongly associated with recurrent or late-stage cervical cancer[10]. HER family members share three domains with each other, each of which has a similar structure. These structures involve an extracellular region, the purpose of which is to play a role in binding and recognising ligands and activating the receptor; a transmembrane region, which is implicated in receptor interactions; and finally, an intracellular region of the TK domains which contains the enzymatic activities of the TKs that act on intracellular adaptor proteins[11-13]. Each receptor has a specific ligand, including TGFRα

Table I. EGF receptor and ligands

EGF Receptor	EGF Ligands
(ErbB-1)	EGF TGF-α Bidirectional regulation factor Epigen β-cyctosine HBGF Epiregulin
HER2/neu (ErbB-2)	none
HER3 (ErbB-3)	Neuregulin1 Neuregulin2
HER4 (ErbB-4)	β-cyctosine HBGF Epiregulin Neuregulin1 Neuregulin2 Neuregulin3 Neuregulin4 Tomoregulin

heparin-binding EGF (HB-EGF), EGFR, amphiregulin (AR), neuregulin (NRG), epigen (EPG), betacellulin (BTC), and epiregulin (EPR)[8].

These ligands are laid out in Table I, while receptors and their corresponding ligands, target therapies, and dimerization options are laid out in Figure 2. Figure 3 describes the signalling pathways activated by EGFR, including the Ras/Raf/MEK, and PI3K pathways.

HER1/EGFR

Recently, EGFR TK domain mutations and EGFR gene amplification have been implicated in recurrent or late-stage cervical cancer. HER-family proteins form homo- or heterodimers following ligand binding, with each dimer possessing different affinities and signalling properties[14]. Upon activation, the singular form of EGFR/HER1 transitions into a homodimer that is active[15]. The HER-family

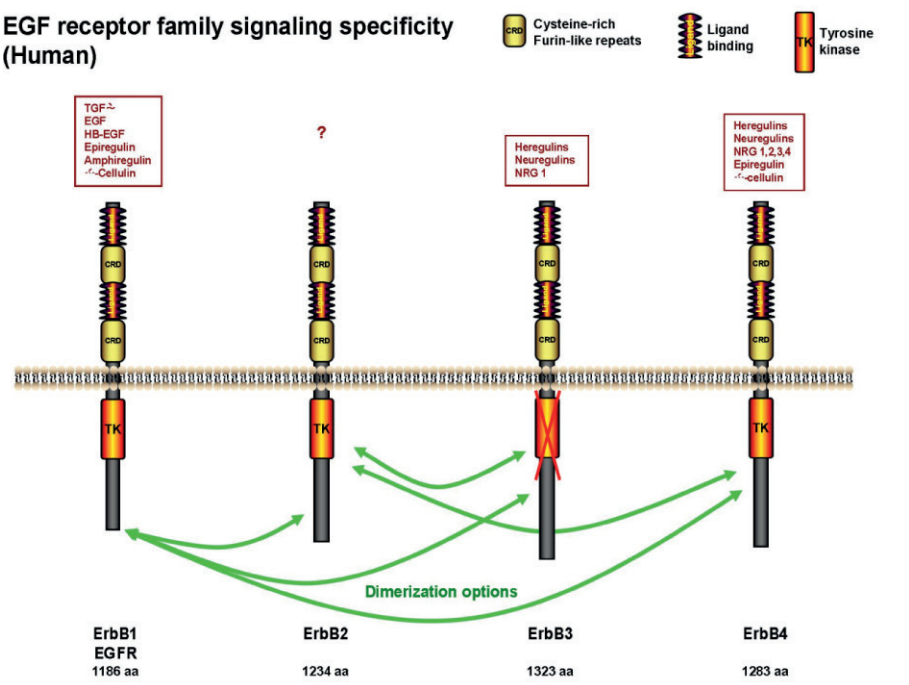

Figure 2. The HER/ErbB signalling network. It is usually the case that the HER signalling pathways are implicated in cell growth and cell survival regulation, differentiation, adhesion, angiogenesis, and migration. The members of the HER family are as follows: (i) EGFR/HER1; (ii) HER2; (iii) HER3; and (iv) HER4. In addition, ErbB-1 is another name for EGFR/HER1, ErbB-2 for HER2, ErbB-3 for HER3, and ErbB-4 for HER4. EGF ligands bind with their receptors, forming various ErbB dimers. After the activation of the receptor, a range of molecules (indicated by the purple colour) are recruited in a direct way to the ErbBs with enzymatic or adaptor functions. In turn, they contribute to the activation of downstream signalling components (indicated by the blue colour), which modifies the activity of several nuclear transcription factors (indicated by the yellow colour).

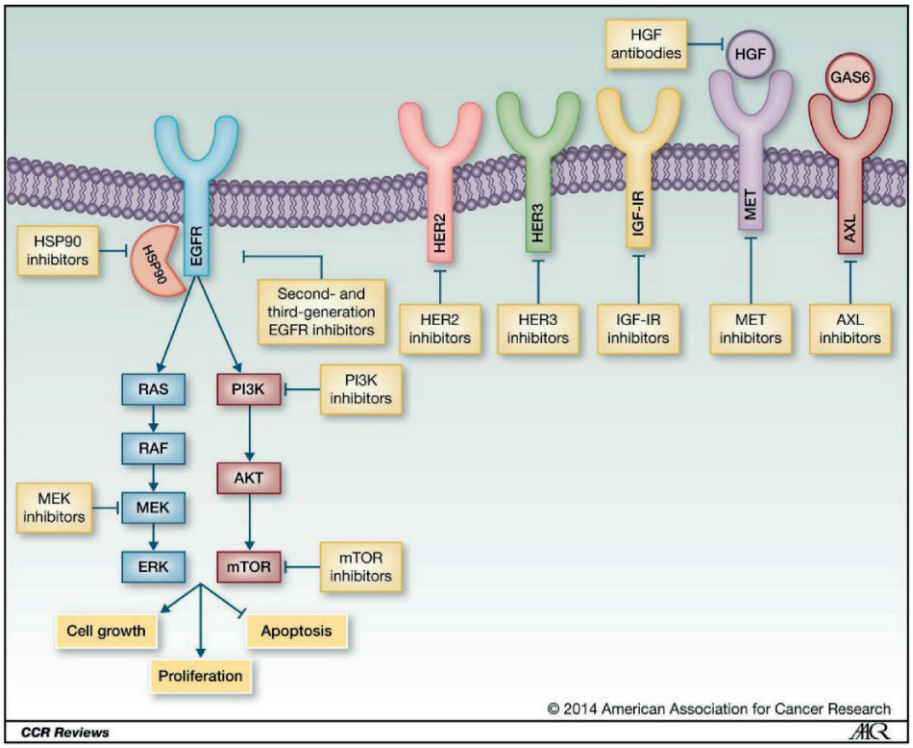

Figure 3. Signal transduction by the HER family. Typically, HER signalling pathways are implicated in cell growth regulation, cell proliferation, and programmed cell death. The purpose of the present figure is to summarise the interactions that occur among the JAK/STAT, MAKP, and PI3K/AKT pathways. MAKP greatly increases transcriptional activation by STAT, and although EGFR/HER1 is not able to facilitate the activation of the PI3K/AKT pathway in a direct manner, it attaches to the ras/MAKP pathway and the ras/PI3K/AKT pathway. AXL is a gene that has arisen as an important contributing factor for drug resistance and immune escape in cancer cells, and so it plays a role in producing metastatic cancers characterised by strong aggression. Transcription factor downregulation, where these are needed for the EMT extracellular matrix, occurs as a consequence of AXL knockdown. The MET signalling pathway performs a critical function in the migration of cells, apoptosis, differentiation, and proliferation. Additionally, it increases aggressive cell phenotype formation for tumour cells to promote the survival and invasion of these cells and avoid immunity.

receptor's hetero-dimerisation or homo-dimerisation (EGFR-HER2 or EGFR-EGFR, respectively) leads to the activation of kinase domains within the cell, in turn contributing to the transphosphorylation of tyrosine residues and the stimulation of various downstream effector molecules. The survival and growth of carcinoma cells seem to be maintained by a network of HER-family receptors and ligands. Therefore, the total HER receptor expression levels, as well as tumour cell ligands, could determine the response to HER inhibitors[16].

HER2, HER3, and HER4

When compared to different family members, no studies have linked HER2 ligands to others[8]. Furthermore, in the absence of ligand binding, it is not possible for HER2 to dimerise. When HER2 is partnered with different members of the HER family, its activation can occur *via* heterotypic interaction with different HER receptors[17]. NRG is directly bound to HER3 and HER4. The phosphorylation of different proteins is not an ability of unbound HER3, which requires transphosphorylation by binding with various HER receptors, operating like a kinase-impaired protein. HER3 is associated with tumour drug resistance, metastasis, and growth[18]. HER4 has structural similarities to other members of the HER family and binds to ligands including NRG-2 and NRG-3. HER4's defining characteristics are antiproliferation and proapoptotic activities[19].

HER Pathway Synergy

HER pathway synergy is closely related to tumour progression[20]. This synergy provides an "escape route" which inhibits specific HER-family members, but this can be compensated for with parallel HER pathways[21]. Compared to single-re-

ceptor inhibitors, cancers that target various areas on the HER pathway are more efficient at blocking tumour growth.

The Molecular Mechanism of the HER Family Receptor in Tumour Development

At the outset, it is worth noting that ErbB-1 is another name for EGFR/HER1, ErbB-2 for HER2, ErbB-3 for HER3, and ErbB-4 for HER4. As referenced above, each protein consists of three different domains: extracellular, membrane-spanning sequence, and intracellular domain[22]. HER-family receptors block TK phosphorylation through the intracellular domain containing the ATP binding site. As an orphan receptor, it is only possible for HER2/ErbB-2 to contribute to the transduction of signals through the formation of heterodimers with different members of the family. In addition to the fact that innate tyrosine kinase activity is not present in HER3/ErbB-3, inactive homodimers are present. The three most common heterodimers are ErbB1/ErbB-4, ErbB-2/ErbB-4, and ErbB-2/ErbB-3[23]. Tyrosine phosphorylation, innate protein TK activity activation, and activation of signal transduction pathways occur after the dimerisation of receptors. Cases in point include the ras/raf/MEK/MAPK pathway and the phosphatidylinositol 3-kinase (PI3K)/AKT pathway[24]. HER signalling pathways are usually involved in cell growth regulation[25].

Due to evidence that the over-expression of HER ligands is strongly implicated in the development of tumours in human beings, invasive potential of cancer cells, enhanced chemotaxis, and higher microvessel density in tumours, HER ligands are a key focus in cancer therapy research[8]. Zhang et al[26] analyzed 273 cervical cancer tissue samples and found aberrant inactivation of EGFR in recurrent or late-stage cervical cancer. A potential mechanism to account for this was EGFR promoter methylation. A fundamental consideration in cancer prognoses for patients with cervical cancer is the issue of characterising EGFR methylation status. Resistance to therapeutic interventions that seek to inhibit EGFR may correspond to EGFR hyper-methylation. Moreover, they could impact cervical cancer's clinical course[27]. Several studies of patients suffering from breast cancer have shown that tumours defined as positive with respect to HER2 display a link to unfavourable prognoses[8]. Additionally, mortality in patients with squamous cell carcinomas of the head and neck has been found to correlate strongly with HER3 expression. As such, HER3 may represent a promising target for cancer immunotherapy[8].

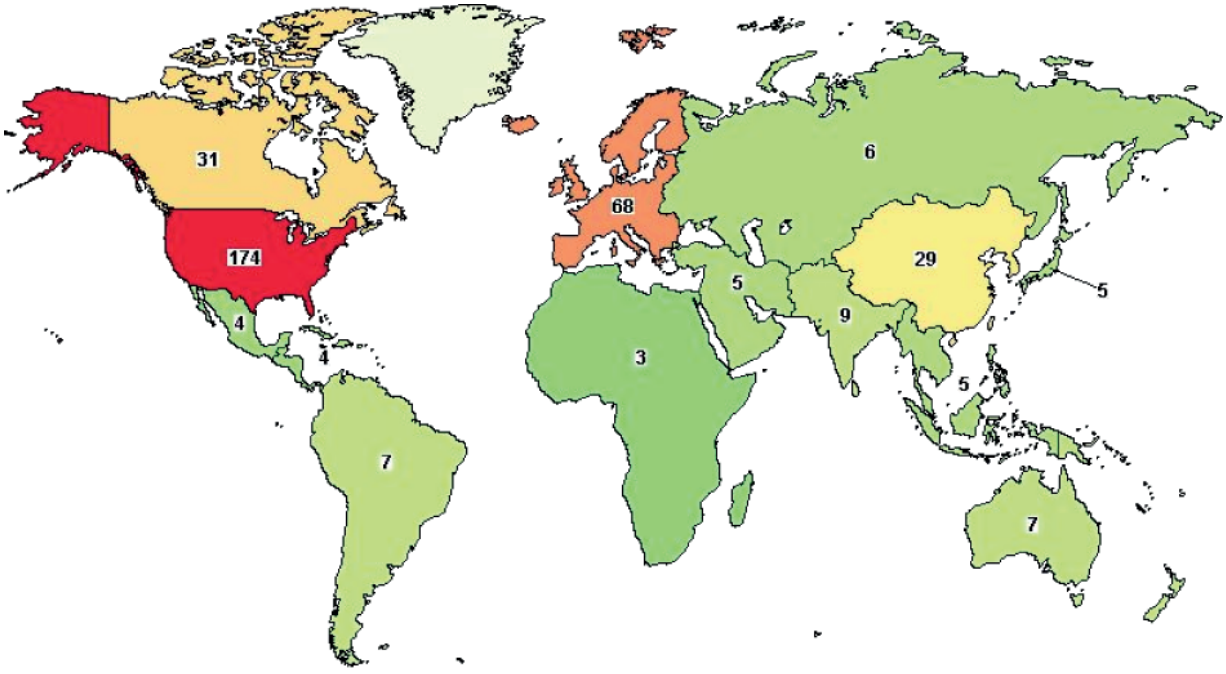

Figure 4. Targeting therapy in cervical cancer (registered on the official website, clinicaltrials.gov). Exclusion of research projects lacking locations took place from the map or in counts. Inclusion of research projects with several locations took place for every area containing the location.

Table II. The HER-directed TKIs (tyrosine kinase inhibitors) reviewed in this study.

Drug Target Cancer	Reversible Refs
Gefitinib EGFR NSCLC, esophageal cancer, metastatic head and neck cancer	Reversible [60-65]
Erlotinib EGFR NSCLC, pancreatic cancer	Reversible [50-54]

Results

Recent HER Inhibitor Developments Based on Clinical Trials

Current developments in HER inhibitor therapy have tended to focus on small-molecular drugs, including tyrosine kinase inhibitors, as well as monoclonal antibodies that are chimeric/humanised[28]. In the case of tyrosine kinase inhibitors, which are commonly referred to as TKIs and include erlotinib and gefitinib, these are used for various cancer treatments, particularly NSCLC therapies[8], as shown in Table II. Targeting of the fourth domain of the HER2 receptor's extracellular segment is the hallmark of trastuzumab, the monoclonal antibody. This drug was the first to receive clinical approval for treating HER2-related conditions by targeting the HER2 pathway[8]. As a chimeric human-murine monoclonal anti-EGFR antibody, cetuximab plays a role in competing against ligands for the EGFR extracellular domain. This inhibits EGFR's tyrosine kinase activation[29], as shown in Table III. Figure 4 shows some approaches for anti-HER targeting therapies for cervical cancer.

The complex nature of cancer-related molecular mechanisms, along with their role in inhibiting the effectiveness of drugs with only one agent, has been confirmed by clinical data. In view of this, the importance of targeting various members in the HER3 family with respect to the PI3K/Akt/mTOR cascade is essential[30]. Recent research has confirmed the clinical benefits of using neratinib and trastuzumab for the dual inhibition of HER proteins relating to metastatic patients who have received substantial pre-treatment.

Drawing on a sample of participants suffering from solid, advanced tumours, a phase I combination trial was undertaken to focus on neratinib and an mTOR inhibitor. Despite the strong successes of targeted therapy using trastuzumab and other monoclonal antibodies, many patients experienced recurrence following the therapeutic intervention. Researchers have proposed other potential mechanisms of anti-HER receptor resistance, including aberrant expression of HER proteins, crosstalk in HER proteins, expression P13CA mutations[31], epithelial-to-mesenchymal transition (EMT)[8], and the reduction of phosphatase and tensin homologue (PTEN). In the case of the latter, this has been identified as a gene that suppresses tumours. Generally, pathway suppression can induce compensatory activation of other pathways. When pan-HER inhibitors inhibit several pathways, this could be an effective way to avoid therapeutic resistance.

The Potential Clinical Prospects of Pan-HER Inhibitors in Recurrent or Late-Stage Cervical Cancer

As discussed above, when compared to single mAbs, pan-HER inhibitors can more efficiently inhibit proliferation and reduce levels of HER proteins. At the same time, pan-HER inhibitors have been shown to reduce basal levels of EGFR hetero-dimerisation and EGFR homo-dimerisation, irrespective of the availability of ligands. Notably, this is not observed in regard to individual mAbs. Irreversible inhibitors can help fight drug resistance, although the potential advantages of the new drugs with this mechanism (efficacy, within-class selectivity, ability to overcome competition) are counteracted by intrinsic liabilities (thyroid function, hypothyrea, glycometabolism)[32]. EGFR hyper-methylation, as mentioned above, can be associated with therapeutic resistance to EGFR inhibition for recurrent or late-stage cervical cancer. Pan-HER inhibitor treatment has

Table III. Monoclonal antibodies currently approved or being investigated that target HER-family receptors.

Name	Type	Source	Target	Use
Trastuzumab	mAb	Humanized	HER2	Breast cancer
Cetuximab	mAb	Chimeric	EGFR	Cervical cancer and head and neck cancer

Table IV. Important ongoing clinical trials with Pan-/dual HER-targeted therapies.

Conditions	Trial	Phase	Sample size	Design
Neratinib-based trials				
Solid tumors and BC	NCT00741260	1/2	105	Neratinib + Capecitabine
	NCT03065387	1/2	20	Neratinib + Everolimus, Palbociclib or Trametinib
Advanced Cancer HER2/HER3/EGFR-mutated				
Amplified solid tumors	NCT01953926	2	392	Neratinib ± Paclitaxel
Glioblastoma	NCT02977780	2	280	Neratinib + Temozolomide
Poziotinib-based trials				
HER2+ Metastatic BC	NCT02659514	2	70	Poziotinib
NSCLC with EGFR or HER2 Exon 20	NCT03318939	2	174	Poziotinib

All the relevant information of clinical trials was registered on the official website (clinical trials.gov). BC (breast cancer), NSCLC (non-small cell lung cancer).

proved effective in recurrent and late-stage cervical cancers that induced EGFR gene hyper-methylation and amplification[33].

When a specific member of the HER family is targeted, this can upregulate different members, thereby inducing plasticity and heterogeneity. Studies have evaluated the impact of several pan-HER inhibitors, including those that target HER4, HER2, and HER1, and phase I testing was recently completed. As the majority of pan-HER inhibitors are administered orally, patients with high acceptance rates and good tolerance are ideal, meaning clinical use is more convenient. Table IV provides details regarding trials with pan-HER-targeted interventions, which are currently underway.

Discussion

Due to the complex nature of the molecular mechanisms that underpin the progression of cancer, paired with single-agent drug limitations, some researchers have drawn attention to the possibility of targeting several members of the HER family in the PI3K/Akt/mTOR cascade. By contrast, single targeting approaches of HER signalling pathways have not yet given rise to optimal outcomes, and this is also true for cell lines that are sensitive[8]. Pan-HER inhibitor therapies involving various combinations of targeted therapies, radiation, and chemotherapy are under investigation[34].

Wang et al[8] suggested that a combination of HER and VEGFR could promote anti-tumour effects in ovarian cancers. The higher production of HER ligands has been linked to radiotherapy-induced recovery of tissue, with the potential ramifications of this increase including cell senescence, higher apoptosis, and redistribution of the cell cycle. When tissue regeneration is inhibited following radiotherapeutic or surgical interventions, this leads to the stimulation of signalling pathways and, in turn, promotes recurrence[8].

Pan-HER inhibitors, when combined with chemotherapy, have been demonstrated to achieve synergistic results in preclinical studies and in clinical trials. Variations in the combinations of therapeutic modulations may allow for greater control over tumour growth levels when compared to conventional agents alone, particularly for advanced-stage cases of cervical cancer[33]. Furthermore, combination of HER inhibitors with glycolysis blockers could overcome the putative HIF1-α-mediated resistance to HER-targeted therapies. Therefore, we could propose that the use of HER inhibitors in association with glucose uptake blockers can be a potentially effective treatment option for HER-positive cervical cancer patients[35].

Conclusions

Recently, researchers have increasingly addressed small-molecule TKIs' potential to permeate the blood-brain barrier, thereby modulating CNS metastasis. Trastuzumab and lapatinib were effective for CNS metastasis[8] and resulted in improved survival rates for patients with CNS metastases. However, due to elongated periods of time and reduced frequencies, some researchers

have reported on progressive CNS recurrences. Neratinib ATP-binding cassette barrier 1 (ABCB1), a pan-HER inhibitor, reversed ABCB1-mediated resistance, a protein transporter found at the blood-brain barrier, which was not the case for lapatinib and trastuzumab[8]. Further research is needed to verify the extent to which pan-HER inhibitors are more effective at permeating the blood-brain barrier when compared to single agents that target HER.

In summary, *in vitro* and *in vivo* results indicate that HER inhibitor treatments, particularly those that draw on pan-HER inhibitors, are associated with wide-ranging efficacy for anti-tumour treatments. Pan-HER inhibitors have been shown to improve prognoses for recurrent or late-stage cervical cancer patients. Preclinical studies show promising results, as well as the potential to improve results for recurrent or late-stage cervical cancer patients. Pan-HER inhibitors have also shown synergistic results in clinical and pre-clinical settings when combined with chemotherapy. Combination with radiotherapy, however, requires more long-term analysis. Areas of future interest are various, but should include research into the efficacy of pan-HER inhibitors in penetrating the blood-brain barrier, particularly when considered in relation to single agents that target HER. This will be explored in clinical trials involving patients with cervical cancer.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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