ErbB Targeted Therapy in Endometrial Cancer

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Abstract

The potential role of ErbB receptors (especially EGFR and ErbB-2) as targets for cancer therapy has been investigated for over 30 years.

Anti-ErbB monoclonal antibodies (MoAbs) bind to the extracellular domain of EGFR or ErbB-2 and prevent ligand binding and receptor activation. They are an attractive and appropriate treatment option in patients with advanced, recurrent or metastatic endometrial cancer and with EGFR and ErbB-2 overexpression.

ErbB-specific tyrosine kinase inhibitors (TKIs) block the binding of ATP to the intracellular domain of EGFR and/or ErbB-2 and prevent tyrosine kinase activity and subsequent intracellular signaling. They are another attractive and appropriate treatment option in patients with advanced, recurrent or metastatic endometrial cancer and with EGFR and ErbB-2 overexpression.

The overall response rate to ErbB targeted therapies is modest, unless they are associated with chemotherapy or radiotherapy. Moreover, molecular targeted therapies have still shown modest effect in unselected endometrial cancer patients.

Perhaps ErbB-targeted therapies may be used as adjuvant treatment in type II endometrial cancer patients with EGFR and ErbB-2 overexpression.

Classification

ErbB targeted therapies classified into 2 main categories: [7, 8]

Anti-ErbB Monoclonal Antibodies (MoAbs)

1. Anti-EGFR MoAbs: cetuximab, panitumumab. They bind to the extracellular domain of EGFR on the surface of tumor cells [7-9]. Subsequently they prevent ligand binding and ligand dependent receptor activation [7-9]. Moreover they prevent receptor-ligand internalization [8].

2. Anti-ErbB-2 MoAbs: trastuzumab, pertuzumab. They bind to the extracellular domain of ErbB-2 on the surface of tumor cells [7-9]. Trastuzumab prevents ligand independent receptor activation, but the exact mechanism of action is subject of debate [7-9]. Pertuzumab prevents receptor homodimerization and heterodimerization [7-9].
ErbB-specific Tyrosine Kinase Inhibitors (TKIs)

1. EGFR TKIs: gefitinib, erlotinib. They block the binding of ATP to the intracellular tyrosine kinase domain of EGFR in tumor cells [7-9]. They prevent tyrosine kinase activity and subsequent intracellular signaling [7-9]. Gefitinib and erlotinib are reversible TKIs [9].

2. EGFR and ErbB-2 TKIs: lapatinib, afatinib. They block the binding of ATP to the intracellular tyrosine kinase domain of EGFR and ErbB-2 in tumor cells [7, 8]. They prevent tyrosine kinase activity and subsequent intracellular signaling [7, 8]. Moreover, dual TKI overcome the potential for redundancy in receptor signaling pathways [8]. Lapatinib is reversible TKI, while afatinib is irreversible TKI [9].

Effectiveness in Endometrial Cancer

Anti-ErbB Monoclonal Antibodies (MoAbs) in endometrial cancer

Anti-ErbB MoAbs may be an attractive and appropriate treatment option in patients with advanced, recurrent or metastatic EC and with EGFR and ErbB-2 overexpression [10-15].

A phase II study (NCT00392769) evaluated the efficacy of cetuximab in unselected patients with advanced or recurrent EC [16, 17]. Unfortunately, that study failed to demonstrate significant activity of cetuximab [16, 17]. In the study population, the partial response rate was 5% [17].

The clinical efficacy of trastuzumab has been reported in several case reports, in patients with advanced, recurrent or metastatic EC and with ErbB-2 overexpression [10, 18-20]. In those cases trastuzumab used as single agent or in combination with chemotherapy demonstrating significant activity. [10, 18-20].

A phase II study of Gynecologic Oncology Group (GOG-181B) evaluated the efficacy of trastuzumab as single agent in unselected patients with advanced or recurrent EC and with ErbB-2 overexpression [21]. Unfortunately, that study failed to demonstrate significant activity of trastuzumab [21]. Perhaps, this may be attributed to problems in the study design [20]. In the study population, the partial response rate was 0% [21].

An ongoing randomized phase II study (NCT01367002) evaluates the efficacy of carboplatin/paclitaxel with or without trastuzumab in selected patients with advanced or recurrent type II EC (papillary-serous) and with ErbB-2 overexpression [22].

ErbB-specific Tyrosine Kinase Inhibitors (TKIs) in endometrial cancer

ErbB-specific TKIs may be another attractive and appropriate treatment option in patients with advanced, recurrent or metastatic EC and with EGFR and ErbB-2 overexpression [11-15, 23-26].

A phase II study of Gynecologic Oncology Group (GOG-229C) evaluated the efficacy of gefitinib as single agent in unselected patients with persistent or recurrent EC [26]. Unfortunately, that study failed to demonstrate significant activity of gefitinib [26]. In the study population, the complete response rate was 4.1% and the progression free survival ≥6 months was 16.6% [26].

A phase II study (NCIC IND-148) evaluated the efficacy of erlotinib as single agent in unselected patients with advanced or metastatic EC [25]. Unfortunately, that study failed to demonstrate significant activity of erlotinib [25]. In the study population, the partial response rate was 12.5% [25].

A phase II study of Gynecologic Oncology Group (GOG-229D) evaluated the efficacy of lapatinib as single agent in unselected patients with persistent or recurrent EC [24]. Unfortunately, that study failed to demonstrate significant activity of lapatinib [24]. In the study population, the partial response rate was 3.3% and the progression free survival ≥6 months was 10% [24].

Effectiveness in well-defined subgroups of endometrial cancer

Molecular targeted therapies have failed to demonstrate significant activity in unselected EC patients [11-15, 23-27]. Overall response rate to these drugs is modest, unless they are associated with chemotherapy or radiotherapy [7].

ErbB-targeted therapies have not clinically tested in type II EC [28]. Perhaps ErbB-targeted therapies may be used as adjuvant treatment in type II EC patients with EGFR and ErbB-2 overexpression [10, 12-15, 18, 19, 28-35].

Especially the role of ErbB-targeted therapies in selected EC patients, should be further investigated in clinical trials [10, 11, 14, 15, 20, 21, 23, 25, 28, 35-38]. Moreover further studies into the molecular pathways of EC, may increase our knowledge and lead to the discovery of new generation molecules with higher therapeutic efficacy [11, 13-15, 38].

References

[14.] Androuopoulos G, Adonakis G, Liava A, Ravazoula P, Decavalas G (2013) Expression and potential role of ErbB receptors in type II endometrial can-