Juniper Publishers
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Journal of
Gynecology and Women's Health

Editorial
Volume 1 Issue 1 - February 2016

J Gynecol Women's Health

Endometrial Cancer Treatment: New Insights into the Role of Erbb Receptors

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Submission: February 10, 2016; **Published:** February 17, 2016

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Editorial

The epidermal growth factor system (EGF system) has considerable role in cell proliferation, differentiation and apoptosis. Moreover, it is present in various human organs during embryogenesis and postnatal development [1,2]. However, the dysregulation of the EGF system signaling network involved in the pathogenesis of various diseases [1,3-16].

Especially in cancer, the EGF system has crucial role with a lot of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation) [3,17-19]. In this light, ErbB receptors (especially EGFR and ErbB-2) considered as targets for cancer treatment for more than 30 years [20]. Nevertheless, the significance of ErbB receptors in endometrial cancer (EC) treatment, has not determined yet [4-16].

To begin with, the anti-EGFR Monoclonal Antibodies (MoAbs) (cetuximab, panitumumab) bind selectively the extracellular domain of EGFR on tumor cell surface. Subsequently they prevent ligand binding and ligand dependent receptor activation [20-22]. Furthermore, cetuximab and panitumumab prevent receptor-ligand internalization [21]. The anti-EGFR MoAbs represent an attractive treatment option, especially in patients with advanced, recurrent or metastatic EC and EGFR overexpression [4-16,23].

A phase II study (NCT00392769) evaluated the efficacy of cetuximab in unselected patients with advanced or recurrent EC. However, this study failed to demonstrate significant activity of cetuximab [24,25]. Moreover, the partial response rate in the study population was only 5% [25].

Likewise, the anti-ErbB-2 MoAbs (trastuzumab, pertuzumab) bind selectively the extracellular domain of ErbB-2 on tumor cell surface. However, trastuzumab prevents ligand independent receptor activation with an undetermined mechanism of action. On the other hand, pertuzumab prevents receptor homodimerization and heterodimerization [20-22]. The anti-ErbB MoAbs represent an interesting treatment option in patients with advanced, recurrent or metastatic EC and ErbB-2 overexpression [4,6,10-12,23].

The clinical role of trastuzumab has been reported in several individual cases with advanced, recurrent or metastatic EC and ErbB-2 overexpression. In these cases trastuzumab used either as single agent or in combination with chemotherapy, demonstrating significant activity [23,26-28].

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 ErbB-2 overexpression. Nevertheless, the study failed to demonstrate significant activity of trastuzumab [29]. Perhaps, the study design was responsible for the final results [28]. Additionally, the partial response rate in the study population was slightly more than 0% [29].

Nowadays, 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 ErbB-2 overexpression [30].

On the other hand, the EGFR Tyrosine Kinase Inhibitors (TKIs) (gefitinib, erlotinib) prevent ATP binding to the intracellular tyrosine kinase domain of EGFR in tumor cells. They also prevent tyrosine kinase activity and subsequent intracellular signalling [20-22]. It is worth noting that gefitinib and erlotinib are reversible TKIs [22]. The EGFR TKIs represent another equally attractive treatment option, especially in patients with advanced, recurrent or metastatic EC with EGFR overexpression [4-16,23,31-33].

A phase II study of Gynecologic Oncology Group (GOG-229C) evaluated the efficacy of gefitinib as a single agent in unselected patients with persistent or recurrent EC. Nonetheless, the study failed to demonstrate significant activity of gefitinib. In the study population, the complete response rate was almost 4.1% and the

progression free survival ≥6 months was approximately 16.6% [33].

A phase II study (NCIC IND-148) evaluated the efficacy of erlotinib as a single agent in unselected patients with advanced or metastatic EC. However, the study failed to demonstrate significant activity of erlotinib. The partial response rate in the study population was about 12.5% [32].

In the same way, the EGFR and ErbB-2 TKIs (lapatinib, afatinib) prevent ATP binding to the intracellular tyrosine kinase domain of EGFR and ErbB-2 in tumor cells. They also prevent tyrosine kinase activity and subsequent intracellular signalling [20,21]. It is interesting to note that lapatinib is reversible TKI, while afatinib is irreversible TKI [21,22]. The EGFR and ErbB-2 TKIs represent another attractive treatment option in patients with advanced, recurrent or metastatic EC with EGFR and ErbB-2 overexpression [4-16,23,31-33].

A phase II study of Gynecologic Oncology Group (GOG-229D) evaluated the efficacy of lapatinib as a single agent in unselected patients with persistent or recurrent EC. The study failed to demonstrate significant activity of lapatinib. In the study population, the partial response rate was almost 3.3% and the progression free survival ≥6 months was about 10% [31].

During the last decade, molecular targeted therapies have failed to demonstrate significant activity in unselected EC patients [1,3-16,34]. These therapies have modest overall response rate, unless they are associated with chemotherapy or radiotherapy [20].

It is worth noting that ErbB-targeted therapies have not evaluated clinically in patients with type II EC [35]. Perhaps ErbB-targeted therapies can be used as an adjuvant treatment in selected patients with type II EC and EGFR and ErbB-2 overexpression [1,3-16,23,26,27,35-41].

In conclusion, the efficacy of ErbB-targeted therapies should be further investigated with prospective randomized clinical trials in carefully selected subgroups of EC patients [4,5,10,12 ,13,23,28,29,32,35,42,43]. Moreover, further studies into the molecular pathways of EC, will increase our knowledge and lead to the discovery of new generation molecular targeted therapies [4,5,10-12].

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How to cite this article: Androutsopoulos G, Decavalas G. Endometrial Cancer Treatment: New Insights into the Role of Erbb Receptors. J Gynecol Women's Health. 2016; 1(1): 555552. DOI: 10.19080/JGWH.2016.01.555552

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How to cite this article: Androutsopoulos G, Decavalas G. Endometrial Cancer Treatment: New Insights into the Role of Erbb Receptors. J Gynecol Women's Health. 2016; 1(1): 555552. DOI: 10.19080/JGWH.2016.01.555552