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International Journal of Clinical Therapeutics and Diagnosis (IJCTD)
ISSN 2332-2926

ErbB Targeted Therapy in Endometrial Cancer

Review Article

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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.

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Received: December 24, 2014
Accepted: January 28, 2015
Published: February 04, 2015

Citation: Androutsopoulos G, Michail G, Adonakis G, Decavalas G (2015) ErbB targeted therapy in endometrial cancer. *Int J Clin Ther Diagn.* S1:002 5-7. **doi: http://dx.doi.org/10.19070/2332-2926-SI01002**

Introduction

The epidermal growth factor system (EGF system) is present in various human organs [1, 2]. It has important role in cell proliferation, differentiation and apoptosis during embryogenesis and postnatal development [1, 2].

Dysregulation of the EGF system signaling network is involved in cancer, diabetes, autoimmune, inflammatory, cardiovascular and nervous system disorders [1,3].

Especially in cancer, the EGF system signaling network becomes hyperactivated with a variety of mechanisms (ligand overproduction, receptor overproduction, constitutive receptor activation) [3-5]. Furthermore, the EGF system in cancer contributes in proliferation, transformation, angiogenesis, migration and invasion [6].

The potential role of ErbB receptors (especially EGFR and ErbB-2) as targets for cancer treatment has been investigated for over 30 years [7].

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

[1]. Uberall I, Kolar Z, Trojanec R, Berkovcova J, Hajduch M (2008) The status and role of ErbB receptors in human cancer. Exp Mol Pathol 84(2):79-89.
[2]. Casalini P, Iorio M, Galmozzi E, Menard S (2004) Role of HER receptors family in development and differentiation. J Cell Physiol 200(3):343-50.
[3]. Marmor M, Skaria K, Yarden Y (2004) Signal transduction and oncogenesis by ErbB/HER receptors. Int J Radiat Oncol Biol Phys 58(3):903-13.
[4]. Yarden Y (2001) The EGFR family and its ligands in human cancer. signalling mechanisms and therapeutic opportunities. Eur J Cancer 37 Suppl 4:S3-8.
[5]. Salomon D, Brandt R, Ciardiello F, Normanno N (1995) Epidermal growth factor-related peptides and their receptors in human malignancies. Crit Rev Oncol Hematol 19(3):183-232.
[6]. Holbro T, Civenni G, Hynes N (2003) The ErbB receptors and their role in cancer progression. Exp Cell Res 284(1):99-110.
[7]. Baselga J, Arteaga CL (2005) Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. J Clin Oncol 23(11):2445-59.
[8]. Lurje G, Lenz HJ (2009) EGFR signaling and drug discovery. Oncology 77(6):400-10.
[9]. Tebbutt N, Pedersen M, Johns T (2013) Targeting the ERBB family in cancer: couples therapy. Nat Rev Cancer 13(9):663-73.
[10]. Santin A, Bellone S, Roman J, McKenney J, Pecorelli S (2008) Trastuzumab treatment in patients with advanced or recurrent endometrial carcinoma overexpressing HER2/neu. Int J Gynaecol Obstet 102(2):128-31.
[11]. Adonakis G, Androutsopoulos G (2012) The role of ErbB receptors in endometrial cancer. In: Saldivar J, editor. Cancer of the uterine endometrium - advances and controversies: InTech 23-38.
[12]. Androutsopoulos G (2012) Current treatment options in patients with endometrial cancer. J Community Med Health Educ 2(12):e113.
[13]. Androutsopoulos G, Adonakis G, Decavalas G (2014) ErbB targeted therapy in endometrial cancer. In: Farghaly S, editor. Endometrial cancer: current epidemiology, detection and management: Nova Science Publishers.
[14]. Androutsopoulos G, Adonakis G, Liava A, Ravazoula P, Decavalas G (2013) Expression and potential role of ErbB receptors in type II endometrial can-

cer. Eur J Obstet Gynecol Reprod Biol 168(2):204-8.
[15]. Androutsopoulos G, Michail G, Adonakis G, Decavalas G (2014) Molecular biology, expression and clinical significance of ErbB receptors in endometrial cancer. Hel J Obst Gynecol.
[16]. Trials NC (2006) Phase II study of cetuximab (erbitux) in patients with progressive or recurrent endometrial cancer. http://clinicaltrials.gov/show/NCT00392769.
[17]. Slomovitz B, Schmeler K, Miller D (2010) Phase II study of cetuximab (Erbitux) in patients with progressive or recurrent endometrial cancer [abstract]. Gynecol Oncol 116(suppl 1):S13.
[18]. Jewell E, Secord A, Brotherton T, Berchuck A (2006) Use of trastuzumab in the treatment of metastatic endometrial cancer. Int J Gynecol Cancer 16(3):1370-3.
[19]. Villella J, Cohen S, Smith D, Hibshoosh H, Hershman D (2006) HER-2/neu overexpression in uterine papillary serous cancers and its possible therapeutic implications. Int J Gynecol Cancer 16(5):1897-902.
[20]. Santin A (2010) Letter to the Editor referring to the manuscript entitled: "Phase II trial of trastuzumab in women with advanced or recurrent HER-positive endometrial carcinoma: a Gynecologic Oncology Group study" recently reported by Fleming et al., (Gynecol Oncol., 116;15-20;2010). Gynecol Oncol;118(1):95-6.
[21]. Fleming G, Sill M, Darcy K, McMeekin D, Thigpen J, et al. (2010) Phase II trial of trastuzumab in women with advanced or recurrent, HER2-positive endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 116(1):15-20.
[22]. Trials NC (2011) Evaluation of carboplatin/paclitaxel with and without trastuzumab (Herceptin) in uterine serous cancer. http://clinicaltrials.gov/ct2/show/NCT01367002.
[23]. Androutsopoulos G, Michail G, Adonakis G, Decavalas G (2014) ErbB receptors and ErbB targeted therapies in endometrial cancer. J Cancer Ther 5(6):483-92.
[24]. Leslie K, Sill M, Lankes H, Fischer E, Godwin A, et al. (2012) Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. Gynecol Oncol 127(2):345-50.
[25]. Oza A, Eisenhauer E, Elit L, Cutz J, Sakurada A, et al. (2008) Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. J Clin Oncol 26(26):4319-25.
[26]. Leslie K, Sill M, Fischer E, Darcy K, Mannel R, et al. (2013) A phase II evaluation of gefitinib in the treatment of persistent or recurrent endometrial cancer: a Gynecologic Oncology Group study. Gynecol Oncol 129(3):486-94.
[27]. Hogberg T (2011) What is the role of chemotherapy in endometrial cancer? Curr Oncol Rep 13(6):433-41.
[28]. Konecny G, Santos L, Winterhoff B, Hatmal M, Keeney GL, et al. (2009) HER2 gene amplification and EGFR expression in a large cohort of surgically staged patients with nonendometrioid (type II) endometrial cancer. Br J Cancer 100(1):89-95.
[29]. Konecny G, Venkatesan N, Yang G, Dering J, Ginther C, et al. (2008) Activity of lapatinib a novel HER2 and EGFR dual kinase inhibitor in human endometrial cancer cells. Br J Cancer 98(6):1076-84.
[30]. Vandenput I, Vanden Bempt I, Leunen K, Neven P, Berteloot P, et al. (2009) Limited clinical benefit from trastuzumab in recurrent endometrial cancer: two case reports. Gynecol Obstet Invest 67(1):46-8.
[31]. El-Sahwi K, Bellone S, Cocco E, Cargnelutti M, Casagrande F, et al. (2010) In vitro activity of pertuzumab in combination with trastuzumab in uterine serous papillary adenocarcinoma. Br J Cancer 102(1):134-43.
[32]. Elsahwi K, Santin A (2011) ErbB2 overexpression in uterine serous cancer: a molecular target for trastuzumab therapy. Obstet Gynecol Int 2011:128295.
[33]. Fader A, Santin A, Gehrig P (2013) Early stage uterine serous carcinoma: management updates and genomic advances. Gynecol Oncol 129(1):244-50.
[34]. Gadducci A, Tana R, Cosio S, Fanucchi A, Genazzani A (2008) Molecular target therapies in endometrial cancer: from the basic research to the clinic. Gynecol Endocrinol 24(5):239-49.
[35]. Androutsopoulos G, Decavalas G (2013) Management of endometrial cancer. International Journal of Translation & Community Medicine 1(1):101.
[36]. Odicino F, Bignotti E, Rossi E, Pasinetti B, Tassi R, et al. (2008) HER-2/neu overexpression and amplification in uterine serous papillary carcinoma: comparative analysis of immunohistochemistry, real-time reverse transcription-polymerase chain reaction, and fluorescence in situ hybridization. Int J Gynecol Cancer 18(1):14-21.
[37]. Roque D, Santin A (2013) Updates in therapy for uterine serous carcinoma. Curr Opin Obstet Gynecol 25(1):29-37.
[38]. Adonakis G, Androutsopoulos G, Koumoundourou D, Liava A, Ravazoula P, et al. (2008) Expression of the epidermal growth factor system in endometrial cancer. Eur J Gynaecol Oncol 29(5):450-4.

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