

## HER2/neu as a Prognostic Marker and Therapy Target in Prostate Cancer

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### ABSTRACT

Prostate cancer is a most common endocrine tumor in men and about every one from six men in northern countries is under the risk of this tumor in old ages. Most common problem in treatment of PC is the development of androgen resistance, the mechanisms of which are not yet completely understood. HER2 may have a role in development of androgen independence, metastasis and prognosis of prostate cancer (PC). HER2 also serves as a molecular target in PC therapy. Different therapeutic strategies are investigated for HER2 targeted therapy in PC. More studies need for the evaluation of diagnostic, prognostic and therapeutic value of HER2 in PC.

**KEYWORDS:** *prostate cancer, androgen resistance, HER2*

Prostate cancer is a most common endocrine tumor in men and about every one from six men in northern countries is under the risk of this tumor in old ages [1,4,18]. Treatment of prostate cancer (PC) (surgery, chemo-, hormone and radiotherapy) is less effective and in most cases is directed to palliative results [18].

Most common problem in treatment of PC is the development of androgen resistance, the mechanisms of which are not yet completely understood [18,31,36]. However, studies performed in the last years have shown that androgen receptor mutations, gene amplification and alterations in growth-factor receptors may play a key role in the progression to androgen-independent, hormone-refractory PC [3,11]. The significance of epidermal growth factor receptors (EGFR) is well established in most common tumor of women - breast cancer. Over expression of HER2/neu (c-erb B-2) proto-oncogene, which belongs to EGFR family, is presented in 25-30 % of breast and ovarian cancer cases and is associated with hormone independence and poor prognosis [4,19]. There are evidences of the effectiveness of trastuzumab (HER2/neu targeted monoclonal antibody) in treatment of breast cancer - especially, in combination with chemotherapy [20]. Despite this, the results about the over-expression of HER2/neu in PC and its prognostic and targeting significance are controversial. Therefore, in this review we have received the problems related to the importance of the HER2/neu in PC diagnosis, prognosis and treatment.

### THE BIOLOGY OF HER RECEPTORS

HER2 (c-erb B-2) encodes the 185 kDa transmembrane tyrosine kinase receptor gene [1,17]. It belongs to the HER family consisting with four genes encoding four homologous HER receptors: erb B-1/HER1, erb B-2/HER2, erb B-3/HER3 and erb B-4/HER4. These receptors interact with EGF, transforming growth factor alpha, heparin binding EGF, amphiregulin, epiregulin, betacellulin and neuregulins 1, 2, 3 and 4 [5,17]. The HER receptors have a similar structure - cysteine-rich extra cellular ligand-binding domain, a lipophilic transmembrane part, and an intracellular signal-transducing tyrosine kinase domain [8,34]. HER2 receptors exists as monomers and they are activated by their ligands, forming homodimers and heterodimers, with the exception of HER3, which is kinase inactive. Activation of the receptors by dimerization leads to antiphosphorylation of intracellular tyrosine residues that, in turn,

stimulate substrate binding and initiation of specific signaling cascades [5,17].

HER 1 binds to several ligands except the neuregulins. HER3 and HER4 bind to neuregulins. No ligand has yet been identified for HER2.

HER receptor ligands by high-affinity site bind to HER1, HER3, or HER4 and by low-affinity site - to HER2. It results in the formation of HER1-HER2, HER2-HER3 or HER2-HER4 heterodimers [5,17]. The heterodimers exhibited high HER ligand affinity as well as more potent biological activity than monodimers, including the proliferate activity characterized to HER2-HER3, a predominant heterodimer in carcinoma cells. HER2 have no ability to bind ligand but by its over-expression tyrosine kinase activity is raising and any ligand stimulation can be enhanced by over-expressed HER2 which is the part of HER1, HER3 or HER4 heterodimers [5,17]. HER2 over-expression inhibits the heterodimers own down-regulation, resulting in increased signaling by HER1, HER4 and can initiate extremely strong mitogenic signals by HER3. When HER2 is normally expressed, ligands binding to HER receptors, form only a few HER2 heterodimers, resulting in normal cell growth by the weak HER2/neu mediated signaling.

### HER2 EXPRESSION IN PROSTATE CANCER

HER2 is over-expressed in 20% to 30% of human breast and ovary cancers and is associated with poor prognosis for the patient [9,19,40]. The clinical trials of HER2 targeted diagnosis and therapy now are under way in non-breast tumors too, because it is established that EGFR over-expression characterizes epidermal and squamous cell carcinomas, non-small cell lung cancer and gliomas. The ERBB2 gene over-expression in these tumors has also been considered as a negative prognosis marker [2]. In PC cases, as well as in most other non-breast cancer cases too, FISH and IHC results of HER2 over-expression are not related to each other [19,40,41]. It has shown by Vernimmen et al. that different mechanisms are involved in erbB-2 gene over-expression in breast and in other cancers and additional studies are needed to understand the mechanisms responsible for the increased of the erbB-2 transcription and protein over expression in non-breast cancer cells [41].

By the results of Jorda et al it seems that the percentage of c-erbB-2-positive cases among untreated prostate cancer patients is lower than in breast cancer [17]. By the mean of some authors HER2 has a role in progression and androgen independence of prostate cancer and

moreover, it can serve as an independent prognostic marker of androgen independence, metastasis process and poor prognosis [11,13,15,27,29,32,34]. Lee et al have shown that the erb B-2 signal is involved in regulating the secretion of PSA by androgen-independent human prostate cancer cells [24]. Like this, Shi et al have shown, that HER2/neu expression is strongly associated with androgen independence and with Gleason score in untreated localized primary prostate cancer [36]. Zellweger et al have found that HER2 together with p53, Bcl-2, Syndecan-1 and EGFR are preferentially expressed in hormone-refractory and metastatic prostate cancer [44]. Ross et al., have demonstrated that HER2 gene amplification by FISH (41% of PC) correlated with tumor grade and DNA ploidy status, but HER2/neu protein over expression by IHC (29% of PC) correlated only with tumor grade [28]. Liu et al concluded that low level of HER2 gene amplification has implications for the direction of current and planned clinical trials of trastuzumab in advanced prostate cancer [25]. According the results, received by Lara et al., HER2/neu is over expressed infrequently in patients with prostate carcinoma and large amounts of patients are available for the HER2 targeted therapy studies [21,22]. Mark et al have found, that HER2/neu amplification detected in prostate cancer seem to be lower than those in most cancers that they studied and HER2/neu amplification does not seem to play as significant a role [26]. Calvo et al reported, that HER2 protein and message over expression and HER2 amplification were not found in Al-CaP [8]. Hernes et al agree that during the development of AIPC increases c-erb B-1 positivity and HER2 positivity is associated with shorten survival [17]. Opposite to all above mentioned authors, Gu et al concluded, that HER2 is over expressed in 100% of PC and in 20% of prostate benign hyperplasia [16]. The following explanations are offered for this discrepancies: firstly, it is the heterogeneity of cancer cell population in biopsies from human PC; secondly, there may be differences in the pattern of HER2 between PC tissue and in metastatic cancer tissue; thirdly, several methodological differences may lead to variability of IHC results. Recently Sanchez et al. [32] have shown, that IHC analysis of HER2 in prostate cancer needs modified, organ-specific system of methods, but we could not found other publications (by these authors or by others) yet, which would confirm this evidence. Carles et al concluded, that prostate carcinoma is a dynamic process and therefore HER2/neu expression is a dynamic process too [10]. Thus, we must conclude that about the expression of HER2 in PC yet are more questions than answers.

#### HER2 TARGETED THERAPY IN PC

Current approaches to target HER2 pathways include down regulation by adenoviruses, antisense oligonucleotides, ribozine and tyrosine kinase inhibitors. Effective approach to control cell proliferation is to use the growth factor receptor-blocking monoclonal antibody. Humanized form of 4DS monoclonal antibody, trastuzumab (herceptin) now is intensively used against breast tumors over-expressing HER2 receptors. Clinical trials of HER2 targeted therapy against other solid tumors (including prostate cancer) are now under way [2,4,19].

Recently Lara et al. from their phase II trial have not found FISH amplification in PC tissue samples and over expression HER2 by IHC was infrequent. HER2 over

expressed patients did not respond to trastuzumab alone [21,22]. Ziada et al. from their phase II trial including 18 patients with HRPC concluded that trastuzumab in monotherapy regimen has poor efficacy [45].

Agus et al., in their preclinical PC model have shown that herceptin is effective only in hormon-dependent PC xenografts [3]. These authors in more recently published work note that by the use of 2C4 monoclonal antibody the inhibition of ligand-dependent erbB2 signaling occurs in both, low and high erb-B2 expressing systems. They demonstrate that in vitro and in vivo growth of several breast and prostate tumor models is inhibited by 2C4 treatment [4]. Herceptin can be effectively used for the treatment of PC in combination with taxanes [38].

Yang et al. demonstrated that ABX-EGF a fully human anti-EGF receptor monoclonal antibody might be effectively used as a monotherapy agent [43].

In animal studies HER2 targeted therapy of PC is effective by specific vaccination [6,7], by HER2 Bi-armed activated T cell therapy [12]. HER2 receptors are down regulated by interferon-gamma [32] and by ansamycin antibiotics too [39]. In HER2 positive prostate cancer treatment might be effectively used oncotoxins [36].

HER2 over expression is related to the increase of vascular endothelial growth factor (VEGF) expression [23], PSA level elevation [24] and consequently, anti-VEGF therapy may be effectively used in HER2 positive PC as well as anti-PSA therapy too.

#### DISCUSSION

By the results of Ross and al [30] FISH is more sensitive than IHC in detecting HER2/neu gene abnormalities, predicts postoperative disease recurrence, and may prove important in planning therapy for patients with prostate carcinoma but taking ahead the results of most other authors we must conclude like Calvo et al [8], that studies of HER2 protein expression or gene amplification in clinical PC report conflicting results and have failed to establish clearly that HER2 is important in PC progression, androgen independence and as a therapeutic target [8].

However, there are some findings, which make reasonable the future investigations of HER2 and other epidermal growth factors as a prognostic factors and therapeutic targets in PC. Firstly, one of the indirect mechanisms of androgen receptor signaling modulation is its enhancement through the activation of peptide growth factors and cytokines. After androgen withdrawal, increased interleukin 6 secretion and HER2/neu over-expression are associated with the progression to hormone-refractory prostate cancer, indicating that IL-6 and HER2/neu may protect prostate cancer cells from death [29]. Secondly, HER2, through the HER1, HER3, or HER4 heterodimers enhances signaling of EGF and can initiate extremely strong mitogenic signal by HER3 [5]. It is clear that we are needing in more studies of detection of HER2 positive cells in blood [1,35], by modified IHC method [32], during the dynamism of prostate cancer progression [10] with other molecular markers [14,44] to decide this problem.

The role of HER2 in cancer cell is depended not only on its tyrosine kinas activity, but also by EGF receptors (HER1, HER2, HER3) too. Consequently, the full EGF monoclonal antibody must be effective against HER2 over-expressing

cancer cells. Some experimental studies have shown the effectiveness of full EGF monoclonal antibodies against PC [17,43]. There are some bi-specific monoclonal antibodies, which are effective, both in experimental and clinical studies against HER2 over-expressing PC [12,33]. HER2 receptor over-expression is reflected by IFN-g too, and may be it will be reasonable to combine HER2 specific monoclonal antibodies with IFN-g [33].

Most of clinical studies with monotherapy of PC with herceptin have not shown its effectiveness, but herceptin was effectively used in combination with taxanes [21,38, 45]. One of the explanations of this phenomenon may be the over-expression of an antiapoptotic oncogene BC1-2 in PC. Some authors have shown the correlation of over

expression of HER2 and BCL-2 [44], but in other studies this correlation was not found [14].

Other HER2 targeted therapy strategies are the use of HER2/neu peptide-based vaccines; recombinant oncotoxines [37] and immunotherapy by activating of T cell mediated immunity, or with cytotoxic lymphocytes engineered to express chimerical receptors recognizing HER2/neu [5, 40].

In conclusion we must say that the studies about the role of HER2 in PC are very important and HER2 may play the role in prognosis and development of PC and in Future treatment strategies. We are in need of more studies for the decision of these questions.

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## **HER2/neu как прогностический фактор и терапевтическая мишень при раке предстательной железы**

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### **Р Е З Ю М Е**

Рак предстательной железы является самой распространенной эндокринной опухолью у мужчин. В северных странах в старческом возрасте каждый шестой мужчина подвержен риску развития рака предстательной железы. Основной проблемой при лечении этой болезни является развитие андрогенной резистентности, механизмы которой все еще не выяснены. Существует мнение о значении HER2 в развитии андрогенной резистентности и метастазировании при раке предстательной железы. HER2 может служить как в качестве прогностического фактора, так и терапевтической мишени у подобных больных. С этой целью и разрабатываются различные терапевтические стратегии, необходимые для дальнейшего исследования и оценки диагностического, прогностического и терапевтического значения HER2 при раке предстательной железы.

**Ключевые слова:** *рак простаты, андрогенная резистентность, HER2*