

Profiling serum HER-2/NEU in prostate cancer

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Abstract

One of the four transmembrane receptors that belong to the erB family, is the HER2/neu oncoprotein. It forms heterodimers by binding to specific ligands, enhancing cell signaling and assisting in cell growth and differentiation. A variety of human epithelial tumors are characterised by an overexpression and gene amplification of the HER2/neu oncoprotein. This is the case of breast tumors, in which the receptor's overexpression and its gene have been studied extensively and its overexpression has been associated with unfavorable prognosis.

In addition, HER2/neu plays a major role in understanding the oncogenesis of prostate adenocarcinoma. For this reason, clarifying the HER2/neu expression is particularly important in androgen independent prostate cancer (PCa), due to the increasing interest in using anti-HER2 targeted therapies for advanced disease treatment. On the other hand, the overexpression of HER2/neu has been reported to release soluble extracellular domain (ECD) in the serum of PCa patients. For this reason, the present review focuses only on studies referring to Serum HER2/neu levels in PCa patients. Serum levels of HER2/neu generally increase with advanced disease state and higher levels have been associated with recurrent or metastatic PCa and a clinically worse outcome. Therefore, it may be concluded that since there is a correlation between increased HER2/neu levels and a poor prognosis in prostate adenocarcinoma, serum HER2/neu could be used in clinical practice and follow up of patients with advanced PCa. Hippokratia 2013, 17, 2: 108-112

Keywords: HER2/neu oncoprotein, prostate cancer, serum, ECD, metastatic, advanced disease

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Introduction

Prostate Cancer (PCa) is the most common malignancy among men in most of Western countries¹. The incidence of PCa varies among different countries with the highest rates reported in North America, Australia and northern and central Europe while the lowest rates are reported in south-eastern and south central Asia and northern Africa.

Usually, increased initial PSA levels present a worse cause-specific survival rate for PCa patients and many of them, with increasing PSA values, develop extra capsular disease or evidence of bone metastatic involvement². For this reason, serial PSA measurements can assist in monitoring disease progression.

On the other hand, conventional pre-treatment modalities, such as bone scan, computed tomography (CT) and magnetic resonance imaging (MRI) often fail to detect early dissemination of microscopic metastatic disease which unfortunately, leads to biochemical recurrence of PCa³⁻⁴. For most patients with locally advanced or metastatic PCa, hormonal therapy remains the primary and most important treatment, resulting in PSA reduction

and symptomatic improvement⁵. However, in almost all of these cases, PCa finally progress to hormone independence⁶⁻⁷. The mutations and androgen receptor's overexpression are among the most important mechanisms involved in the growth of androgen-independent PCa⁸. In one third of advanced prostate tumors however, no discernible androgen-receptor mutation or amplification has been reported, therefore implying a potential role of non-androgenic growth factors⁹⁻¹⁰. On the other hand, the main factors affecting PCa disease outcome are the stage, Gleason score and PSA levels. But, PSA as an independent tumor marker for PCa, has limitations in its sensitivity and specificity¹¹⁻¹³. For these reasons, the necessity of identifying improved prognostic biomarkers becomes obvious, in order to recognize disease progression and optimize therapeutic decisions.

The human epidermal growth factor receptor 2 (HER2/neu) is an oncoprotein, which belongs to the EGFR family and plays a major role in proliferation, cell growth and differentiation¹⁴. It consists of an extracellular ligand-binding domain, a transmembrane and an intracellular tyrosine kinase domain. Binding of specific

ligands to the extracellular domain of HER2/neu forms hetero-dimers and that way initiates cell signaling, resulting in inhibition of apoptosis and activation of tumor cell growth and invasion. Over expression of HER2/neu protein and its gene amplification have been related with the progression of many types of tumors¹⁵. About 30% of breast and ovarian cancers overexpress HER2/neu, and anti-HER2/neu treatment has been shown to be very effective strategy when co-administered with other chemotherapeutic agents¹⁶⁻²⁰. Especially, trastuzumab, a monoclonal antibody with high specificity for a HER2/neu epitope, in combination with chemotherapy, presents encouraging results and prolongs survival²⁰.

Despite the receptor's clinical importance for breast cancer, the role of HER2/neu in PCa is still controversial²¹⁻²³. Evidence, however, suggests that it may contribute to androgen independence and in identifying patients more likely to present disease progression²⁴⁻²⁹. Nishio Y, et al considered that "HER2/neu overexpression, may be useful as a marker of an unfavorable prognosis by predicting the interval until relapse and the outcome in bone metastatic PCa patients after endocrine therapy"³⁰. Consistent with that, Morote J, et al agreed that "in cases with disease relapse HER2/neu overexpression was associated with poor prognosis" and their results suggest that HER2/neu causes cancer cells to proliferate more aggressively³¹.

In PCa, steroid hormones and growth factors play a regulatory role in cell proliferation and HER2/neu has been associated with activation of androgen-receptor pathways. So, it has been proposed as a survival factor for PCa cells during hormone-refractory disease progression³²⁻³⁴. Indeed, several studies reported that HER2/neu (as measured by immunohistochemistry) is associated with lower survival rates^{21,30,35}. According to a large review, Neto AS, et al reported that in PCa patients with high HER2/neu overexpression, the recurrence rate and risk of death was increased ($p < 0,0001$)³⁶.

Therefore, HER-2 inhibition becomes a possible

treatment strategy for hormone-refractory PCa patients³⁷⁻³⁹. Unfortunately, its efficacy has yet to be proven in clinical practice.

HER2/neu in serum of PCa patients

As previously mentioned, HER-2/neu consists of an intracellular, a transmembrane and an extracellular domain (ECD). HER-2 ECD can be detected in the serum of PCa patients. Increased ECD values usually correlate with a clinical outcome, suggesting a more aggressive tumor growth and metastasis⁴⁰⁻⁴¹. Taking these facts into account, the current review was limited to studies referring to HER2 ECD levels in the serum of patients with advanced PCa, thus enhancing its prognostic implications.

As far as early prostate cancer stages are concerned, the correlation between PCa and BPH, is without statistical significance ($p > 0.05$) and ECD values do not appear to be elevated⁴²⁻⁴³. More specifically, in a recent study with 227 untreated patients with localized PCa, Shariat SF, et al reported that "plasma HER2/neu levels were elevated in those patients with higher Gleason scores ($p = 0.028$)"⁴⁴. In the same study, a preoperative multivariable analysis showed that HER2/neu values were associated with PSA levels and disease progression ($p < 0.001$ and $p = 0.023$ respectively). Consistent with the above in the review of Neto AS, et al, it was agreed that the percent of patients with Gleason score > 7 was higher in the HER2/neu over expression group ($p = 0.01$) and it varied with different antibodies used³⁶. Moreover, a trend of increasing HER-2 ECD was observed in correlation with higher cancer stages.

Indeed, as Okegawa, et al described, HER-2 was uncommon in the serum of primary untreated PCa⁴⁵. However, serum HER-2 ECD was significantly higher in PCa patients with bone metastatic disease compared with non-metastatic. Their data are in agreement with other published reports showing that serum HER-2 is indeed elevated in metastatic PCa (Table 1). Moreover, higher levels have been associated with hormone-refractory dis-

Table 1: Association between serum HER2/neu levels with other pathological features.

Reference	No metastatic PCa patients	↑ Serum HER2/neu (% or p value)*	HER2/neu vs PSA (p value)	HER2/neu vs Gleason score (p value)	HER2/neu vs biochemical recurrence (p value)
Osman I, 2005 ⁵¹	75	$p = 0.006$	> 0.05	NA	NA
Shin BY, 2002 ⁵²	40	35%	0.013	NA	NA
Okegawa T, 2006 ⁴⁵	70	$p = 0.003$	$> 0.05^{**}$	> 0.05	0.0078
Domingo-Domenech J, 2008 ⁴¹	69	34.8%	0.016	NA	0.007
Tambo M, 2009 ⁴⁹	75	$p = 0.005$	0.017	> 0.05	< 0.001

NA: not available, *: Correlation between PCa patients with vs without metastases, **: Only when PSA range ≤ 20 ng/ml, there was no correlation.

Table 2: Correlation of serum HER2/neu with EOD score.

Reference	HER2/neu cut off point	HER2/neu vs EOD score (p value)
Domingo-Domenech J, 2008 ⁴¹	15ng/ml	0.002
Okegawa T, 2006 ⁴⁵	12.6ng/ml	0.041

Table 3: Increased risk of cause specific death in PCa patients with serum HER2/neu above the cut off values.

Reference	HER2/neu cut off values	p value
Osman I, 2005 ⁵¹	14ng/ml	<0.001
Domingo-Domenech J, 2008 ⁴¹	15ng/ml	<0.0001

Table 4: Association between serum HER2/neu (ELISA) and its tissue expression (IHC, FISH) in PCa.

Reference	No PCa patients	HER2/neu overexpression- IHC positive	ELISA vs IHC (p value)	HER2/neu amplification-FISH
Lara PN, 2002 ³⁷	62	8%	>0.05	Negative
Domingo-Domenech J, 2008 ⁴¹	69	35.3%	0.016	Negative
Tambo M, 2009 ⁴⁹	75	24%*	>0.05	NA

NA: not available, *: Score 1+ or above counted positive.

ease. It seems that overexpression of HER-2 not only activates cell proliferation, but stimulates androgen receptor signaling as well, and renders PCa cells refractory to androgen receptor inhibition^{28-29, 46}.

Correlations with ECD HER2/neu

As shown in Table 1, patients with HER2 ECD values above the cut-off point in each study were at increased risk for recurrence and PSA progression. In addition, HER-2 ECD levels were significantly associated with the extent of bone disease (EOD), according to Soloway's et al method⁴⁷ (Table 2). In that case, it is possible that matrix metalloproteinases are involved in proteolytic cleavage of HER2 ECD into the blood stream, leading to tumor invasion and metastasis⁴⁸. Arai Y, et al reported that "serum HER-2 levels were increased in patients with advanced disease and these patients had a significantly shorter interval to disease progression than those with a normal level"⁴⁶. So, HER-2 ECD might be a factor of unfavorable prognosis in advanced metastatic PCa patients.

The survival rate in relation to HER2 ECD level has been reported only in two studies, and according to Neto AS, et al, on meta-analysis, there seems to be a significant correlation of elevated HER2 ECD values with earlier recurrence and risk of death ($p < 0.007$), (Table 3).

HER2/neu level evaluation included any method, or kit and overexpression in PCa has been associated with a worse clinical outcome. In most of the studies, HER2/neu expression was assessed using immunohistochemistry (IHC). IHC staining was classified into a 0-3+ scale. PCa patients with IHC score of 2+ or above were considered positive to have HER2/neu overexpression. Currently, HER2 ECD expression in PCa (measured by the method

of ELISA) has been the focus of many researchers, but there is limited published data on the association between HER2/neu tissue and serum expression, with conflicting results (Table 4). HER2/neu amplification was not detected in any of them.

According to Tambo M, et al, possible explanations for such discrepancies may be the variability in fixation and staining techniques and the fact that tissue samples collected by biopsy might not reflect the whole tumor status in IHC⁴⁹. In patients with multiple metastases, the heterogeneity of HER2/neu expression may lead to false-negative results. On the other hand, PSA progression may occur as a result of local residual disease or occult nodal disease or present distant metastases during prostatectomy or even a combination of the above. Thus, assays which rely on tissue sampling are inadequate for assessing HER2/neu changes after tumor removal, while ELISA blood sampling techniques allow for real-time effective monitoring of post-treatment HER2/neu status.

In PCa, the prognostic value of HER2 ECD level may reflect the biological behaviour of hormone refractory tumors. So, these patients should be included into anti-HER2/neu clinical trials. But, anti-HER2/neu agents as monotherapy proved to be ineffective in the management of androgen-independent PCa patients, probably because of the interference of monoclonal antibodies with elevated soluble HER2 ECD, or because the introduction of the therapy was too late in the natural history of the disease^{36, 49}. It therefore becomes obvious, that additional research is required in order to prove the effectiveness of chemotherapy, as combined with anti-HER2 agents for hormone refractory PCa⁵⁰.

Conclusions

HER2/neu is mainly overexpressed in more aggressive disease and hormone-independent PCa. Increased HER2 ECD values in the serum correlate with the presence of metastatic disease and may indicate patients with increased risk of death. Therefore, detecting HER2 in serum, as opposed to tumor tissue sampling, is a minimally invasive alternative method of identifying disease progression in PCa patients. More extensive research studies and longer follow ups are required to optimize this assay for application in the clinical setting.

Conflict of Interest

Authors declare that there is no conflict of interest and no funding was received.

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