



Association between HER-2/neu (erbB-2) Overexpression and Biochemical Recurrence of Prostate Cancer after Radical Prostatectomy

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Abstract

Introduction: HER 2 (c-erbB-2) is involved in the prostate cancer development and, more specifically, in the progression of the disease from androgen-dependent to hormone-refractory. The purpose of this study is to assess whether the overexpression of HER 2 (c-erbB2) is associated with the behavior for biochemical recurrence for prostate cancer regarding incidence and the amount of time needed for its manifestation.

Material and Methods: All patients submitted to radical retropubic prostatectomy for prostate cancer in one of the author's private practice (MS) from 1990 to 2012 were recruited. There were found 2,284 patients. Of these patients, were included only the patients whose surgical specimen analysis encompassed the research for HER 2 (erbB-2) expression and with demographic and follow-up data. Therefore, 365 patients were included in the study. The patients were divided in two groups for analysis: those with overexpression of HER2 (erbB-2) and those without it.

Results: The overexpression of HER (c-erbB2) was associated with higher pre-operative PSA ($p < 0.001$), higher Gleason score in the surgical specimen ($p = 0.043$) and percentage of positive fragments at core biopsy ($p = 0.013$). Biochemical recurrence (PSA > 0.2) was more than twice (41.5% vs. 19.8%, $p < 0.001$) more frequent in the patients with HER 2 (c-erbB2) overexpression. Nevertheless, there was no difference in the time for biochemical recurrence ($p = 0.73$). There was little data after recurrence for those patients were forwarded for the clinical oncologist.

Conclusions: In our study sample we found that HER-2 (c-erbB2) overexpression was associated with more biochemical recurrence by more than two fold, even though it takes about the same amount of time for the recurrence to happen.

Keywords: Prostate cancer; HER-2

Introduction

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 characterized 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 has been studied extensively and its overexpression has been associated with unfavorable prognosis [1]. In breast cancer, the role of c-erbB2 role is well known, with its overexpression observed in 20% to 30% of the samples [2].

Although there is consensus about c-erbB2 overexpression in prostate cancer, recent studies have suggested its importance in disease progression to a more aggressive disease, since it was revealed that progression of hormone-dependent disease is associated to increased c-erbB2 levels [3]. It was observed that c-erbB2 expression was associated with higher PSA levels and higher Gleason scores in patients with metastatic disease refractory to hormone therapy. It was thus concluded that c-erbB2 is involved in the prostate cancer development and, more specifically, in the progression of the disease from androgen-dependent to hormone-refractory [4].

The purpose of this study is to assess whether the overexpression of HER2 (c-erbB-2) is associated with biochemical recurrence for prostate cancer regarding incidence and the amount of time needed

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Table 1: Patients' data divided by overexpression of HER2 (cerB-2).

HER-2/neu (erbB-2) overexpression (+2/+3)	Present	Absent	p
n	99	266	
Age (years)	63.6 ± 6.5	63.7 ± 7.2	0.46
Follow-up time (months)	144 ± 18.4	124 ± 21.5	<0.001
Pre-operative PSA (ng/ml)	11.52 ± 8.17	8.26 ± 5.97	<0.001
Gleason score ≤ 6 (surgical specimen)	30	107	0.81
Gleason score >6 (surgical specimen)	69	159	
% of positive fragments at core biopsy	47 ± 45%	35 ± 22%	0.013
Biochemical recurrence n (%)	41 (41.4%)	72 (27%)	<0.001
Time for biochemical recurrence (months)	27.38 ± 27.47	25.67 ± 18.62	0.735
Tumor volume (cc)	3.47 ± 0.79	3.36 ± 0.78	0.23
Prostate size (cc)	19.7 ± 18.8	14.6 ± 12.6	0.003

for its manifestation.

Material and Methods

This was a cross-sectional retrospective study approved by the ethics committee of our institution. All patients submitted to radical retropubic prostatectomy for prostate cancer in one of the author's private practice (MS) from 1990 to 2012 were recruited. There were found 2,284 patients. Of these patients, were included only the patients whose surgical specimen analysis encompassed the research for HER2 (erbB-2) expression and with demographic and follow-up data. Therefore, 365 patients were included in the study.

HER-2 protein expression was determined by IHC using the Hercep- Test kit (DAKO Corp., Carpinteria, CA). Briefly, formalin fixed paraffin sections were deparaffinized in xylene, dehydrated 100% ethanol, and air dried. Antigen retrieval was performed by immersing slides in diluted epitope-retrieval solution, heating them in a water bath at 95°C to 99°C for 40 min, and allowing slides to cool to room temperature. Excess buffer was blotted, and peroxidase-blocking reagent was applied for 5 min. A gentle rinse with distilled water was followed by application of 100 µL of primary antibody (rabbit antihuman HER-2 polyclonal) for 30 min. After rinsing, the slides were incubated for 30 min with 100 µL of visualization reagent. Another rinse was followed by 100 µL of substrate-chromagen solution for 10 min. Sections were then counterstained with hematoxylin, cleared, and mounted. Positive and negative controls supplied in the kit were treated in a similar manner. IHC staining was scored from 0 to 3, in accordance with the HercepTest method. Patients with scores of 2+ or 3+ were considered to have HER-2 overexpression.

The patients were divided in two groups for analysis: those with overexpression of HER2 (erbB-2) and those without it. The data was compared between the two groups with level of significance of 5% with the software StatPlus^v. 2009 for Mac. Categorical variables were analyzed through Chi Square test. Continuous variables were assessed for normal distribution, those with confirmed normal distribution were compared through t-test and those without normal distribution were assessed by Mann-Whitney test.

Results

Patients' data is described in Table 1. There was no difference in the patients' age or tumor volume. The follow-up time for those patients who expressed HER2 (cerB-2) was longer, but both groups were followed for more than 10 years. Prostate size was larger in the

patients that expressed HER2 (cerB-2).

The overexpression of HER (cerB-2) was associated with higher pre-operative PSA ($p < 0.001$) and percentage of positive fragments at core biopsy ($p = 0.013$). There was no association between presence of Gleason >6 on surgical specimen and HER2 (cerB-2) overexpression.

Biochemical recurrence (PSA > 0.2) was more frequent (41.4% vs. 27%, $p < 0.001$) in patients with HER2 (cerB-2) overexpression. Nevertheless, there was no difference in the time for biochemical recurrence ($p = 0.73$). There was little data after recurrence for those patients were forwarded for the clinical oncologist.

Discussion

HER-2 (cerB-2) plays a dual role in the progression of prostate cancer; firstly it may increase the potential of tumor cells to disseminate from the primary tumor via the blood by increasing vascular infiltration. Secondly, in the presence of androgens, there is no survival advantage of expressing HER-2, but once biochemical failure has occurred and androgen blockade started, HER-2 positive cells are resistant to treatment, survive and grow leading to castration resistant disease [5].

Nevertheless, HER-2 (cerB-2) overexpression and mutation has been described in other types of cancer, playing different roles, including gastric, ovarian and salivary gland cancer [6-8]. In non-small cell lung cancer HER-2 (cerB-2) overexpression has been described in over 30% of all patients, but differently from prostate cancer, neither overexpression or mutation were associated with poorer prognosis [9]. Actually, it is plausible that HER-2 (cerB-2) positivity in non-small cell lung cancer can be considered a favorable prognostic factor due to availability of HER2 targeted therapies [10].

In bladder cancer, HER-2 (cerB-2) overexpression is present in about 40% of all patients and is usually associated with higher tumor grades and increased risk for lymph node metastasis [11]. In the remaining sites of the urinary tract such as kidneys and penis, the association between HER-2 (cerB-2) overexpression and different prognosis is poor [12].

A previous meta-analysis described an association between HER-2 (cerB-2) overexpression in the prostatic primary tumor and increased risk of mortality of 1.63. With HER-2 (cerB-2) overexpression the recurrence RR was 1.87 [13]. In our study we found that the overexpression of HER-2 (cerB-2) increased the risk for biochemical recurrence significantly. Nevertheless, taking in consideration the

physiopathology of the overexpression of HER-2 (cerB-2) with prostate cancer, one could assume that biochemical recurrence should be more premature on the patients with its' overexpression, since it is a more aggressive disease, but it was not confirmed by our findings (27.3 vs. 25.6 months, $p=0.73$) [14]. The more likely explanation for this it that the main role of the HER-2 (cerB-2) is set in the androgen-deprivation therapy, where the cells overexpressing HER-2 (cerB-2) are selected over the non-overexpressing ones and in this condition and its' more aggressive behavior is manifested [15].

Our study has one of the largest casuists in the literature so far. Moreover, we have more than 10 years of follow-up of most of our patients', more than observed in most previous studies. Our findings solidify the previous published data regarding incidence of recurrence and greater severity of the disease in the patients with HER 2 (cerB-2) overexpression [13,16].

Regarding limitations, our study presents all the limitation inherent to a retrospective study and also the lack of data after biochemical recurrence, since all our patients were forwarded to the clinical oncologist and, therefore, no more data was available and the assessment of specific or global mortality was not possible.

Much of the physiopathology of HER-2 (cerB-2) overexpression and prostate cancer has been unveiled. Nowadays, great efforts are been made to have a better oncological control of the patients with prostate cancer using the available tools. Recently, several types of immunotherapies have been shown to induce encouraging clinical results, though in a restricted number of patients. There were found correlations between immunologic parameters and clinical outcome in prostate cancer patients who had been vaccinated with a HER-2/neu hybrid polypeptide vaccine (AE37) and received one booster 6 months post-primary vaccinations with improved overall survival [17].

Another approach for immunotherapy has been vaccines for immunoprophylactic prevention of prostate cancer. Although the literature is still scarce on the subject, and the technology is yet in development, these vaccines targeting specific antigens or oncoproteins (erbB2/HER-2/neu) are an exciting proposition, which could translate into a viable reality for clinical application in humans and is one the end-points for all the molecular biology research in prostate cancer [18].

Conclusion

In our study sample we found that HER-2 (cerB-2) overexpression was associated with more biochemical recurrence, even though it takes about the same amount of time for the recurrence to happen. The role HER-2 (cerB-2) overexpression plays seem to be more in the androgen deprivation environment.

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