Plasma Progastrin Level As A Prognostic Biomarker In Advanced Prostate Cancer

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Abstract

Background: Progastrin is a tumor promoting peptide which is detectable in the blood of patients with different cancers. Progastrin gene is a direct target of the WNT/β-catenin oncogenic pathway involved in tumorigenesis and possibly tumor progression/treatment efficacy. Since WNT/β-catenin oncogenic pathway is dysregulated in advanced prostate cancer we evaluated plasma progastrin in metastatic prostate cancer as a predictive and prognostic biomarker.

Methods: Metastatic hormone sensitive prostate cancer (mHSPC) and metastatic castration resistant prostate cancer (mCRPC) states were enrolled in a cohort study of blood sample collection and follow-up for outcomes between 9/2009 and 11/2013. Patients were enrolled in mHSPC unique sub-cohorts before initiating androgen ablation (AA); during AA, at the time of failure of AA and before starting chemotherapy. Plasma progastrin was measured using the ELISA cancerREAD®. Progastrin concentrations in the cancer patients (test set) was assessed against 213 samples from healthy blood donors from the French blood establishment (control set) and progastrin levels were also compared for each of the above four mHSPC and mCRPC cohorts as well as for association with time to failure on AA for the mHSPC cohort and overall survival for both mHSPC and mCRPC subcohorts. We also determined progastrin levels in patients with two serial samples to evaluate if changes were predictive for overall survival.

Results: Of the 523 mHSPC+mCRPC patients 96 were mHSPC before starting AA; 101 mHSPC patients were enrolled during AA; 143 mHSPC patients were enrolled at the time of AA failure and 143 were mCRPC. The median time of follow up of the whole cohort was 8.34 years (IQR: 5.33-12.97) and 371/523 had died at the time of the analysis. Plasma progastrin levels was detected in 87.6% of the patients (cut-off value 1 pM, median value=8.7 pM; IQR 0.211) compared to the control set (median value=0.37 pM; IQR 0.00-1.71). The Receiver Operating Characteristic analysis indicated an area under the curve of 0.84 (p<0.0001; 95% CI 0.81 to 0.87). 246/523 patients had two serial samples analyzed. Of these, 106 patients had a decrease and 140 patients an increase of progastrin levels. Patients with a serial increase of progastrin had a worst overall survival compare to the other group (p=0.019).

Conclusion: Progastrin is a blood based biomarker elevated in advanced prostate cancer patients. Serial increases in progastrin levels during treatment are predictive of poor survival. Progastrin assay might be useful for monitoring therapeutic interventions like androgen deprivation therapy effects as well for advanced prostate cancer patients.

Methods

Patient Methods:

A patient tertiary level, clinically annotated hospital registry with prospective blood/plasma collection from advanced prostate cancer patients between 9/2009 and 9/2013 and uniform sampling was used. Advanced prostate cancer patients were consented and enrolled in different states of progression (metastatic Hormone sensitive PCA (mHSPC) and metastatic castration resistant PCA (mCRPC)).

Analytical Methods:

Plasma EDTA sample was tested in duplicate using 50μl of plasma using cancerREAD lab test (ECS-Progastrin) following manufacturer’s instructions.

Statistical Methods:

Comparisons between groups were performed using the t-test. The statistics were performed with two-sided 5% alpha risks. The Kaplan Meier curves were compared with the logrank test. The following programs were used to perform the statistical analyses; Prism software (GraphPad, La Jolla, CA, USA); SAS version 9.4.9 software. R software version 3.4.4 was used to perform survival curves.

RESULTS

Clinical characteristics of mHSPC and mCRPC patients in screening and follow-up cohort.

Elevated Progastrin Levels In mHSPC And mCRPC Patients

A. Median values of plasma progastrin level in healthy donors and mHSPC and mCRPC patients. B. ROC curve of progastrin for the diagnosis of advanced prostate cancer compared to healthy blood donors.

Progastrin Levels In Different States Of Advanced Pca

A. OS according to progastrin levels evolution during follow-up. Patients with a serial increase of progastrin had a worst overall survival compare to the other group (p=0.019). B. OS according to the timepoints of the blood draw. Patients mCRPC before chechemotherapy” (Point 4a) had a worst overall survival compare to the other group (p=0.046). Cox model for OS shows a significant effect of progastrin levels for the group “mHSPC with PSA relapse on ADT” (Point 3, p=0.0069) but not with the adjusted parameters.

Conclusions

1. Progastrin is a blood-based biomarker in advanced prostate cancer patients.

2. Progastrin is a prognosis biomarker in advanced prostate cancer patients.

3. Progastrin could be used to improve advanced prostate cancer patients follow-up and treatment efficacy monitoring.