DETECTION OF AR-V7 IN PLASMA-DERIVED EXOSOMAL RNA IN METASTATIC PROSTATE CANCER PATIENTS TREATED WITH FIRST-LINE HORMONAL THERAPY

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Introduction: Castration resistance prostate cancer (CRPC) lacks of predictive biomarkers for response and/or resistance to treatment. Recently, it has been found an androgen receptor splice variant (AR-V7), which is associated with resistance to hormonal therapy (Antonarakis et al., 2014). Nowadays, few methods are available to detect AR-V7: tumour tissue, CTCs, or messenger RNA (mRNA) presented in whole blood. Unfortunately, these methods have substantial limitations, such as costs, difficult and long procedures or low sensitivity. Interestingly, we reported previously that AR-V7 splice variant can be detected in RNA extracted from cancer cell vesicles released in blood using digital droplet PCR. In this preliminary investigation, the method was used to predict resistance to second-line hormonal therapy in 36 PC patients, suggesting its clinical relevance and was demonstrated the feasibility, reproducibility and sensitivity of this procedure (Del Re et al., 2016). Concerning the first-line hormonal treatment (abiraterone and enzalutamide) two important clinical trials suggested the benefit in overall survival and radiological progression free-survival in CRPC patients chemotherapy naïve (clinicaltrials.gov NCT01212991, Ryan et al., 2015). However, few studies evaluated the importance of AR-V7 detection at a basal level, prior hormonal treatment (Antonarakis et al. 2017, Bernemann et al., 2016), and are based on CTCs analysis.

Aim: The aim of this study was to evaluate the rate of the AR-V7 positivity by digital droplet PCR in exosomal-derived RNA from plasma samples in CRPC patients candidate to first-line hormonal treatment.

Patients and Methods: Nineteen prostate cancer patients were enrolled in the present study. Plasma samples (3-4 ml) were collected before the beginning of first-line hormonal treatment with abiraterone or enzalutamide or chemotherapy. Exosomes isolation and RNA extraction were performed and tested for analysis of AR-V7 by digital droplet PCR (BioRad®).

Results: Of 19 patients, 16 were treated with abiraterone and 3 with enzalutamide. Median age was 64 yrs (range 48 -81) and 12 patients presented a Gleason Score ≥ 7 (range ≥7-≤9). AR-V7 transcript was detected in 4 patients (21%), with a median range from 90 to 500 copies/ml. The AR-FL transcript was detected in all patients, AR-V7 + (median 4650 copies/ml) and AR-V7 − (median 913 copies/ml), and used as internal control to validate the experiment. The analysis on time to progression (TTP) was not statistically different, even if there was a better survival with AR-V7 - vs. AR-V7 + in a subgroup of patients (7 months vs. 17 months).

Conclusions: These pilot data would characterize the importance of AR-V7 detection in CRPC patients prior start first-line hormonal treatment. Moreover, the usefulness of this biomarker is suggested and the importance of exosomal-RNA as a reliable source of AR-V7 is confirmed.

Reference

Antonarakis et al. (2017) N Engl J Med 371(11):1028–38

Bernemann C et al. (2017) Eur Urol 71(1):1-3.

Del Re et al. (2016) Eur Urol 71(4):680-687

Ryan et al. (2015) Lancet Oncol 16(2):152-60

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