Taxane sensitivity markers in prostate cancer

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Abstract

Background: The results from the CHAARTED and STAMPEDE trials that docetaxel plus androgen-deprivation therapy (ADT) significantly improves survival over ADT alone among men with metastatic, hormone-sensitive and hormone-naïve prostate cancers, represents a potential practice-changing movement. Clinical data exist to support the role of various predictive markers for taxane response, including low or negative class III beta tubulin (TUBB3), positive transducin-like enhancer of split 3 (TLE3) and low or negative p-glycoprotein (PGP/ABCB1). We examined a database of molecularly-profiled prostate cancer patients for taxane sensitivity markers for insight into the mechanism behind the clinical effect of docetaxel.

Methods: 297 patients with prostate cancer were included in the study and tested centrally at a CLIA laboratory (Caris Life Sciences, Phoenix, AZ). Tests included one or more of the following: gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and gene amplification (C/FISH).

Results: In all prostate cases tested, protein levels for taxane markers are: TLE3+ 58.6% (174/297), TUBB3 - 76.8% (228/297) and PGP – 89.9% (267/297). Combined rate of expression (TLE3+/TUBB3-/PGP-) is 41% (121/297), representing a subgroup of patients that may have best responses to taxane therapy. Taxane sensitivity markers by stage and AR status are shown in the table below.

	AR positive		AR negative	
Frequency of Taxane Marker	**Localized**	**Metastatic**	**Localized**	**Metastatic**
TUBB3 -	88% (88/100)	73% (131/180)	75% (3/4)	50% (7/14)
TLE3 +	61% (61/100)	59% 107/180)	17% (1/6)	43% (6/14)
PGP -	87% (87/100)	92% (165/180)	50% (6/12)	86% (12/14)
TUBB3 -/TLE3 +/ PGP -	47% (47/100)	40% (72/180)	0% (0/3)	14% (2/14)
TUBB3 -/TLE3 +/ PGP -	42.5% (119/280)		12% (2/17)	
p-value	P= 0.0113			

Conclusion: Taxane sensitivity markers are observed at a statistically significant higher frequency in AR-positive prostate cancer patients, providing a potential molecular hypothesis for the increased effectiveness of chemo-hormonal therapy observed in hormone-sensitive prostate cancers. A substantial number of both AR positive and negative patients have sub-optimal biomarker profile for taxane responsiveness highlighting an unmet need for on-going drug development in this disease.

Background

- Taxane therapy in combination with androgen deprivation therapy (ADT) has been shown to significantly improve survival in metastatic, hormone-sensitive prostate cancers, over ADT alone.
- Microtubules are highly dynamic tubulin polymers that play a key role during mitosis, organizing and facilitating spindle assembly and function. Taxanes block cell cycle progression through suppression of spindle microtubule dynamics, thus inducing mitotic-slippage and apoptosis.
- Based on the cellular targets of taxanes, several proteins have been implicated in taxane **sensitivity and resistance:**
  - **↓TUBB3** (beta-tubulin 3) is suggestive of response to taxanes**.** *In vitro* data suggests that high levels of **beta**-tubulin 3 could replenish microtubule assembly and overcome the microtubule destabilization induced by taxanes.
  - **↑TLE3** (transducin-like enhancer of split 3) indicates a high fraction of tumor cells are in, making them particularly sensitive to cell cycle perturbation.
  - **↑PGP** (p-glycoprotein) indicates the potential for drug efflux before cellular concentrations of the drug accumulate to induce cytotoxic effects.
- We examined the expression patterns of these biomarkers, and other predictive biomarkers stratified by androgen receptor (AR) status and disease status (metastatic vs. primary).

Methods

297 patients with prostate cancer were included in the study and tested centrally at a CLIA laboratory (Caris Life Sciences, Phoenix, AZ). Tests included one or more of the following: gene sequencing (Sanger or next generation sequencing [NGS]), protein expression (immunohistochemistry [IHC]) and gene amplification (C/FISH). Antibodies and cutoffs for are as follows, or can be obtained by request : AR (AR27; ≥1+ and ≥ 10%), TUBB3 (polyclonal; ≥2+ and ≥ 30%), TLE3 (polyclonal; ≥2+ and ≥ 30%), and PGP (C494; ≥1+ and ≥ 10%). Pearson's chi-squared test (IBM SPSS Statistics, Version 23.0, Armonk, NY) was utilized to test for significant differences between subgroups**. Subgroup stratification for the "Sensitive Profile" is defined as having negative TUBB3 and PGP and positive TLE3, whereas the "Non-Sensitive Profile" is defined as having any degree of expression that is not associated with sensitivity to taxanes (i.e., all other profiles not defined as "Sensitive Profile").**

Results

Table 1. Clinicopathologic Characteristics of Patient Cohort Studied

		AR +					AR -			
	Total n (%)	n	Primary	Metastatic	Median Age [range]	n	Primary	Metastatic	Median Age [range]
Prostate (all)	297 (100)	280	36%	64%	67 [38-88]	17	18%	82%	61 [46-78]
Sensitive Profile	121 (41)	119	39%	61%	68 [45-88]	2	0%	100%	64 [61-67]
P-value	Primary vs. Metastatic: p=0.0008/AR+ vs. AR-: p=0.0113								
Non-Sensitive Profile	176 (59)	161	33%	67%	66 [38-86]	15	20%	80%	60 [46-78]

Table 1- Distribution of disease site utilized for profiling, Androgen Receptor (AR) status and age of patients with prostate adenocarcinomas included in this analysis.

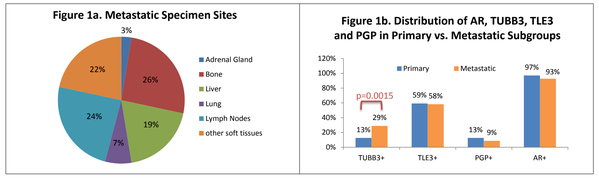


Figure 1a-b– Distribution of metastatic sites for specimens utilized for profiling (n=194) (1a) and distribution of positive expression of TUBB3, TLE3, PGP and AR in primary and metastatic samples (1b).

Results, contd.

Figure 2. Biomarker Profiles of Taxane Sensitive/Non-Sensitive Prostate Cancers compared with Disease Status (A) and AR Status (B).

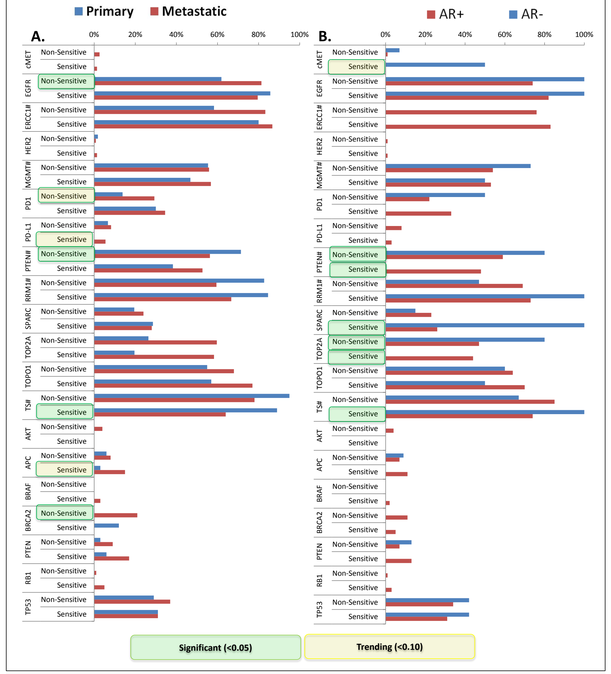
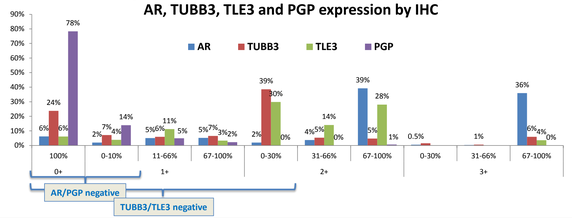


Figure 3. Distribution of Intensity and % Staining of AR, TUBB3, TLE3 and PGP expression by IHC



Results, contd.

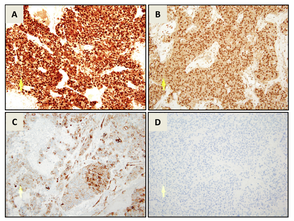


Figure 4A-D. Representative Images of IHC staining for AR, TLE3, TUBB3 and PGP. A. AR staining at 3+ 95%, B. TLE3 staining at 2+ 35%, C. TUBB3 staining at 2+ 20% and D. PGP staining at 0 + 100%.

Conclusions

- Approximately 6-8% of prostate cancers lack androgen receptor expression. AR- patients exhibit a younger median age compared to AR+ patients (61 vs. 67).
- A taxane sensitive profile (defined as TUBB3-/TLE3+ and PGP-) is detected in 41% of all prostate patients and 43% (119/280) in AR+ disease. In contrast, the taxane sensitivity profile occurs at a rate of 12% (2/17) in AR- disease (p=0.01). Proportion of taxane-sensitivity profiles increases in the metastatic setting, compared to primary (39% vs. 61%; p=0.0008).
- 65% of profiling in this cohort is performed on metastatic specimens, with bone specimens being the most commonly submitted (26%), followed by lymph nodes (24%) and liver (19%).
- The frequency of positive expression of AR and taxane markers among primary and metastatic specimens, is evenly distributed, with the exception of TUBB3, for which the frequency increases from 13% in primary to 29% in metastatic prostate cancers (p=0.001).
- Comparisons between patients with sensitive and non-sensitive taxane profiles revealed significant differences in EGFR, PTEN, TS and BRCA2, when layered with disease status. In addition, PTEN, SPARC, TOP2A and TS were significantly different among AR+ vs. AR- patients in various settings of taxane sensitivity.
- These data may have potential implications for treatment combinations and provide clues into the co-occurring alterations that render cells sensitive to taxane therapy.
- Investigation of alternate, non-taxane based treatment options for AR+ metastatic prostate cancer that exhibit a non-sensitive taxane profile may be worthy of further exploration.

References

1. Abal, M., I. Barasoain, et al. (2003). "Taxanes: microtubule and centrosome targets, and cell cycle dependent mechanism of action.
2. Ploussard, G., A. de la Taille, et al. (2010). "Class III B-Tubulin Expression Predicts Prostate Tumor Aggressiveness and Patient Response to Docetaxel-Based Chemotherapy."