Impact of clonal hematopoiesis of indeterminate potential (CHIP) on treatment-related alterations in cardiovascular risk factors for men with metastatic prostate cancer

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Background

- Androgen deprivation therapy (ADT), is the standard first line treatment for metastatic prostate cancer (PC) and associated with worsening of cardiovascular (CV) disease risk factors
- Bipolar androgen therapy (BAT) is a novel treatment for castration-resistant PC that gives supraphysiologic doses of testosterone in conjunction with ADT – rapidly cycling patient testosterone levels (Figure 1). We previously demonstrated that BAT reverses the negative effects of ADT is associated with an improvement in CV risk factors[1]
- CHIP, the expansion of white blood cells with malignancy-associated somatic alterations, is associated with an increased risk of CV disease and is prevalent among men with PC (Figure 2)
- We hypothesized that cardiovascular changes might be influenced by the presence of CHIP, which has previously been associated with an increased risk of cardiovascular disease

Figure 1. BAT and Testosterone

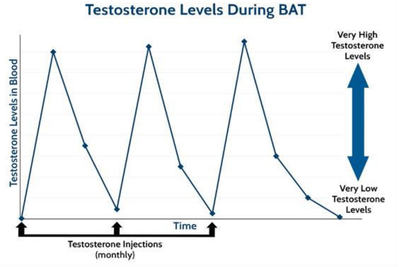
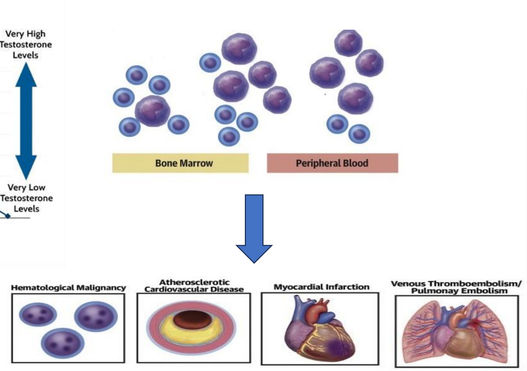


Figure 2. CHIP and Cardiovascular Effects



Methods

- **Population:** Retrospective analysis of the RESTORE clinical trial (NCT02090114) – a study of men with metastatic castration resistant PC, previously treated with ADT and either abiraterone or enzalutamide
- **Treatment:** testosterone cypionate 400mg intramuscularly every 28 days
- **CV risk factors**: Low density lipoprotein (LDL), high density lipoprotein (HDL), and triglyceride (TG) levels were taken at baseline and 3 months after initiation
- **CHIP analysis:** Baseline serum was used to identify presence/absence of CHIP based on whole exome analysis
- **Outcome:** Cardiac events included hypertension, tachycardia, palpitations, pre/syncope, pulmonary embolism, new heart murmurs, myocardial infarction

Results

- CHIP mutations identified were *DNMT3A* (n=4), *TET2* (n=2), *ASXL1* (n=1) and *CSF1R* (n=1)

Table 1. Baseline characteristics by CHIP * P≤ 0.05

Variables (number, %)	CHIP neg (N=52)	CHIP pos (N=7)
Median age at treatment start (years)	72.0	72.0
Race*		
White	48 (92%)	3 (43%)
Non-white	4 (7.7%)	4 (57%)
Prior radiation		
Yes	48 (92%)	6 (86%)
No	4 (7.7%)	1 (14%)
Prior smoking		
Yes	28 (54%)	3 (43%)
No	24 (46%)	4 (57%)
Baseline PSA (ng/mL)	31.7	36.4
Cardiac events		
Yes	14 (27%)	2 (29%)
No	38 (73%)	5 (71%)

CHIP was not associated with an increased risk of CV events or change in LDL, HDL, TG levels among men treated with bipolar androgen therapy (BAT) for metastatic castration resistant prostate cancer

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Table 2. Lipid level changes

Median (range) mg/dL	CHIP neg (N=52)	CHIP pos (N=7)
Baseline LDL	97 (38-160)	100 (63-177)
3-month LDL	86.5 (34-138)	81 (73-131)
Baseline HDL	53 (29-144)	60 (41-111)
3-month HDL	49.5 (29-134)	63 (39-71)
Baseline TG	129 (45-368)	148 (43-342)
3-month TG*	**101.5 (41-333)**	**59 (48-120)**

Figure 3. Survival outcomes by CHIP

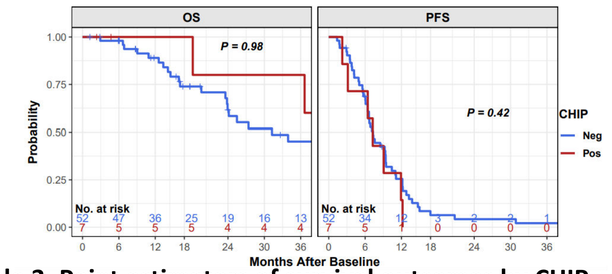

Table 3. Point estimators of survival outcomes by CHIP

	CHIP neg (N=52)	CHIP pos (N=7)
OS		
Number of deaths	27	4
PFS		
Number of progression events	49	7
Median (months)	7.3	7.2
1 year probability (95% CI)	0.25 (0.16, 0.41)	0.14 (0.02, 0.88)

Future Directions

- More research is needed to determine how CHIP influences cardiometabolic risk factors associated with cancer therapies and its clinical impact

References

1. Marshall CH, Tunacao J, Danda V, Tsai HL, Barber J, Gawande R, Weiss CR, Denmeade SR, Joshu C. Reversing the effects of androgen-deprivation therapy in men with metastatic castration-resistant prostate cancer. BJU Int. 2021 Sep;128(3):366-373. doi: 10.1111/bju.15408. Epub 2021 May 7. PMID: 33765326; PMCID: PMC9844547.
2. Kheterpal, SA et al. J Am Coll Cardiol. 2019
3. S Denmeade et al. *Prostate Cancer Foundation*. 2022