Prostate cancer (PC) and homologous recombination repair genes mutations (HRRm): a retrospective, monocentric, observational study aimed at recording histopathological and clinical data and their associations with oncological outcomes

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BACKGROUND

Prostate cancer (PC) is one of the most common tumors worldwide. Although new treatments improved oncological outcomes for metastatic hormone-sensitive prostate cancer (mHSPC) with frontline use of chemotherapy and/or androgen receptor targeted agents (ARTA) in combination with androgen deprivation therapy (ADT), duration of response (DoR) for these treatments is highly variable. The most frequent causes to resistance include androgen receptor (AR) alterations, mutations of the downstream signaling pathways, such as phosphatidylinositol-3-kinase/ protein kinase B (PI3K/AKT), or homologous recombination repair (HRR) genes mutations, including BRCA1 and BRCA2. Recent trials showed prolonged progression-free survival (PFS) and overall survival (OS) in mCRPC with BRCA1/BRCA2 mutations treated with polyADP-ribose polymerase inhibitors (PARPi), leading to increasing interest in this subset of patients and its differences as compared to non HRR-mutated population. This study aimed to evaluate histopathological and baseline clinical characteristics in PC patients with HRR mutations, their prevalence, and clinical outcomes.

MATERIAL & METHODS

From 2019 to 2023, 400 patients with mHSPC have been screened for HRR alterations at the National Cancer Institute of Naples “Fondazione G Pascale”. Mutations in HRR-related genes were identified using archival primary or metastatic tumor samples and/or circulating tumor DNA (ctDNA). They were detected somatic and/or germline mutations in HRR genes in 45 out of 400 patients. We retrospectively analysed clinical and tumor characteristics in this cohort, recording histological features, baseline staging, gene mutations, and medical treatments. We evaluated PFS as oncological outcome.

	Somatic biopsy	Liquid biopsy	Germline
BRCA1	5 (11.1%)	1 (2.2%)	0
BRCA2	21 (46.7%)	6 (13.3%)	8 (17.8%)
ATM	5 (11.1%)	1 (2.2%)	2 (4.4%)
VUS	2 (4.4%)	1 (2.2%)	0
RARE MUT	5 (11.1%)	8 (17.8%)	1 (2.2%)

Tab. 2 – BRCA1, BRCA2 and other mutations in tissue, liquid and germline biopsy

RESULTS

Out of the 400 screened patients, 45 (11%) had at least one mutation, with BRCA2 being the most commonly altered gene (46.7%), followed by BRCA1 (11.1%) and ATM (11.1%). Other rare HRRm were found in 5 patients (11.1%). Median age of patients was 70 years (64 – 74). HRRm were associated with poorly differentiated PC: 32 patients (71.1%) had Gleason score ≥ 8 and, among these, 10 (22.2%) had a Gleason score of 10. 26 patients (57.8%) had metastatic disease at diagnosis, with 18 (40%) having High Volume disease. The most common sites of metastasis were bones and lymph nodes, with only 6 (13.3%) having visceral metastasis. 43 patients (95.5%) received medical treatment for mHSPC with androgen deprivation therapy (ADT) alone (17 pts, 37.8%), ADT plus androgen receptor targeting agents (19 pts, 42.2%), or ADT plus chemotherapy and androgen receptor targeting agents (7 pts,15.5%). Among these, 30 (69.8%) patients experienced disease progression or death resulting in a median PFS of 16.8 months (C.I. 95% 13.7 – 26.2 months), regardless the therapy.

	Overall (N=45)
Median age (range), years	70 (64 -74)
Gleason at baseline	
Gleason 6	1 (2.2%)
Gleason 7	11 (24.5%)
Gleason 8	7 (15.6%)
Gleason 9	15 (33.3%)
Gleason 10	10 (22.2%)
Missing	1 (2.2%)
Histology	
Adenocarcinoma	24 (53.4%)
Acinar	18 (40.0%)
Intraductal	1 (2.2%)
Acinar/Neuroendocrine	1 (2.2%)
Neuroendocrine	1 (2.2%)
Stage at diagnosis, n (%)	
M0	18 (40.0%)
M1 High Volume	18 (40.0%)
M1 Low Volume	8 (17.8%)
Missing	1 (2.2%)

Tab. 1 – Baseline characteristics

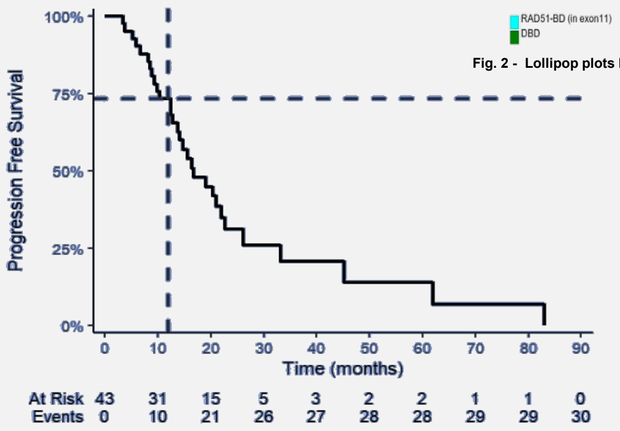

Fig. 1 – Progression Free Survival

Fig. 2 - Lollipop plots by reporting all BRCA1/2 mutations and variants

CONCLUSION

PC with HRRm had more frequently Gleason ≥ 8 and metastases at diagnosis compared to general PC population, according to epidemiological data, confirming the need of early search for mutations in patients with advanced disease and these characteristics. Although the main limit of this pilot study is the small sample size, due to the monocentric design, our results could confirm that HRRm confer a more aggressive PC phenotype and could be associated with poor prognosis. These data support the need for tailoring a specific clinical management of these patients.