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Platinum Priority – Brief Correspondence

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Clinical Features and Therapeutic Outcomes in Men with Advanced Prostate Cancer and DNA Mismatch Repair Gene Mutations

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Abstract

Mismatch repair (MMR) gene mutations are rare in prostate cancer, and their histological and clinical characteristics are largely unknown. We conducted a retrospective study to explore disease characteristics and treatment outcomes of men with metastatic prostate cancer harboring germline and/or somatic MMR mutations detected using clinical-grade genomic assays. Thirteen patients with a deleterious MMR gene mutation were identified. Median age was 64 yr, 75% had grade group 5 (Gleason sum 9 or 10), 23% had intraductal histology, 46% had metastatic disease at initial diagnosis, and 31% had visceral metastases. Most patients (46%) had *MSH6* mutations, 73% demonstrated microsatellite instability, and median tumor mutational load was 18/Mb (range, 3–165 mutations/Mb). Surprisingly, responses to standard hormonal therapies were very durable (median progression-free survival [PFS] of 67 mo to initial androgen deprivation and median PFS of 26 mo to abiraterone/enzalutamide). Two of four men receiving PD-1 inhibitors achieved a $\geq$50% prostate-specific antigen response at 12 wk, with a median PFS duration in these four men of 9 mo. Despite aggressive clinical and pathological features, patients with MMR-mutated advanced prostate cancer appear to have particular sensitivity to hormonal therapies, as well as anecdotal responses to PD-1 inhibitors. Certain histological features (grade group 5, intraductal carcinoma) should prompt evaluation for MMR deficiency. These data are only hypothesis generating.

Patient summary: Prostate cancers with mismatch repair gene mutations have aggressive clinical and pathological features; however, these are very sensitive to standard and novel hormonal therapies, and also demonstrate anecdotal sensitivity to PD-1 inhibitors such as pembrolizumab.

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Owing to the recent Food and Drug Administration's approval of the PD-1 inhibitor pembrolizumab for the treatment of DNA mismatch repair–deficient (dMMR) or microsatellite instability-high (MSI-H) cancers of any histology [1], there has been a renewed interest in identifying tumors with these genomic features to aid therapy selection. However, while MMR deficiency and microsatellite instability are common features of gastrointestinal cancers, MMR gene mutations are rare in prostate cancer, estimated at 2–5% of cases [2,3]. Owing to this low prevalence, data are lacking on the clinical and pathological characteristics of dMMR prostate cancer, and even less is known about the natural history and sensitivity to standard therapies for these cancers. Furthermore, except for isolated case reports (four patients, total) [3–5], there is no documented literature on the responsiveness of dMMR prostate cancers to immune-checkpoint inhibitors.

Here, we aimed to elucidate the clinical and histological features of prostate cancers harboring deleterious MMR gene mutations, with particular attention to potential characteristics that may alert a clinician to consider MMR/MSI testing. We also aimed at describing the sensitivity of MMR-mutated advanced prostate cancers to standard systemic therapies including androgen deprivation, novel hormonal therapies (abiraterone and enzalutamide), chemotherapy (docetaxel), as well as PD-1 inhibitor treatment. We demonstrate that these patients appear to be very sensitive to hormonal therapies but not to chemotherapy and that anecdotal benefits are also observed with PD-1 blockade.

We retrospectively queried our somatic genomic database at Johns Hopkins for prostate cancer cases with pathogenic loss-of-function (ie, inactivating) MMR mutations, and our germline genetic database for similar inherited MMR mutations. Both databases comprise recurrent and/or metastatic prostate cancer cases. Genes of interest included *MSH2*, *MSH6*, *MLH1*, and *PMS2*: the canonical MMR genes [6]. Predicted pathogenic mutations were defined using strict criteria: only protein-truncating mutations (frameshift, nonsense, or splicing lesions) as well as genomic deletions or structural rearrangements were considered deleterious. Somatic next-generation tumor-DNA sequencing had previously been performed for clinical indications using the Personal Genome Diagnostics (PGDx, Baltimore, MD, USA) 125-gene targeted panel [7]. Germline genetic testing was also performed previously for clinical reasons, using the saliva-based 30-gene targeted next-generation panel offered by Color Genomics (Burlingame, CA, USA) [8]. Where available, primary or metastatic tumor tissue was used to perform standard immunohistochemical (IHC) analysis for the detection of the four MMR proteins. Clinical outcomes to a variety of systemic therapies were coded according to the PCWG3 criteria [9]. Prostate-specific antigen (PSA) response evaluation required $\geq$12 wk of follow-up, and the 12-wk PSA response rate is reported.

Thirteen metastatic prostate cancer patients with pathogenic MMR gene mutations were identified: 10 from screening 236 somatic sequencing results (4.2%) and three from screening 348 germline sequencing results (0.9%). Table 1 shows their baseline characteristics. Median age was 64 yr, 69% were white, 75% had grade group 5 (Gleason sum 9 or 10), 23% had intraductal histology, 46% had metastases at initial diagnosis, and 31% had visceral involvement. All patients had received standard androgen deprivation therapy (ADT), 46% (6/13) had received first-line abiraterone or enzalutamide, 15% (2/13) had received docetaxel, and 31% (4/13) had received PD-1 blockade.

Table 2 summarizes the genomic characteristics. Two patients with germline MMR mutations did not have adequate tumor tissue available for somatic DNA analyses or IHC studies, and one additional patient did not have available tissue for IHC studies only. Most men had *MSH6* (46%; 6/13) or *MSH2* mutations (23%; 3/13), and median tumor mutational burden was 18 mutations/Mb (range, 3–165 mutations/Mb). Of those with adequate tissue available for sequencing, 73% (8/11) demonstrated microsatellite instability: 27% (3/11) had no MSI markers shifted, 36% (4/11) had one to two markers shifted, and 36% (4/11) had three to four markers shifted. Median mutational loads were 21 and 6 mutations/Mb for MSI-positive and MSI-negative patients, respectively. While two of three patients with microsatellite-stable status (#2 and #7; both with *PMS2* mutations) had intact MMR protein expression, the third patient (#1) demonstrated loss of MSH2 and MSH6 proteins by IHC consistent with genomic *MSH2* inactivation. Notably, 64% of patients (7/11) had coexisting *TP53* mutations and 36% (4/11) had *TMPRSS2-ERG* fusions.

Despite aggressive clinicopathological features as well as frequent *TP53* mutations, MMR-deficient patients demonstrated high sensitivity to hormonal therapies. All 13 men received standard ADT (without concurrent docetaxel or abiraterone) as initial systemic therapy for metastatic disease, and 85% (11/13) achieved a >90% PSA response (median PSA reduction, 99%), with a median PSA progression-free survival (PSA-PFS) of 55 (95% confidence interval [CI] 50–73) mo and a median PFS of 66 (95% CI 55–77) mo. (By comparison, the median PFS to first-line ADT among 114 MMR-proficient men from our somatic sequencing database with full clinical data was 27 [95% CI 22–32] mo.) Sensitivity to first-line abiraterone or enzalutamide was also high among the six MMR-deficient patients evaluable for this outcome, of whom 83% (5/6) achieved a >50% PSA response (median PSA reduction, 80%), with a median PSA-PFS of 24 (95% CI 5–not reached) mo and a median PFS of 26 (95% CI 6–not reached) mo. (By comparison, the median PFS to first-line abiraterone/enzalutamide among 75 MMR-proficient men from our somatic sequencing database with full clinical information was 12 [95% CI 10–14] mo.) Two MMR-deficient patients received docetaxel, of whom one achieved a >50% PSA response (median PSA reduction, 41%), with a median PSA-PFS of 6 (95% CI 4–9) mo and a median PFS of 7 (95% CI 5–10) mo. Finally, four patients (#6, #8, #9, and #10) received PD-1 inhibitor treatment as fourth- to sixth-line systemic therapy: two using nivolumab and two using pembrolizumab. Half of these patients (two of four [#9 and #10]; both PD-L1 positive by IHC) achieved a >50%

Table 1 – Baseline demographic and disease characteristics of our 13 MMR-deficient prostate cancers

Characteristic	MMR-deficient men (*N* = 13)	MMR-proficient men (*N* = 114)
Age at diagnosis (yr)		
Median (Q1–Q3)	64 (61–70)	63 (59–69)
Race, *N* (%)		
White	9 (69)	99 (87)
Presence of any secondary malignancy, *N* (%)	3 (23)	9 (8)
Family history of cancer, *N* (%)		
First-degree relative	8 (62)	59 (52)
Non–first-degree relative	5 (38)	18 (16)
Gleason sum at diagnosis, *N* (%)		
≤7	2 (15)	30 (26)
≥8	10 (77)	77 (67)
Unknown	1 (8)	7 (6)
Presence of perineural invasion, *N* (%)	4 (31)	68 (60)
Presence of variant histology, *N* (%)		
Ductal/intraductal	3 (23)	14 (12)
Neuroendocrine	1 (8)	0 (0)
Tumor stage at diagnosis, *N* (%)		
T1/T2	3 (23)	36 (32)
T3/T4	10 (77)	78 (68)
Lymph node stage at diagnosis, *N* (%)		
N1	5 (38)	15 (13)
Metastatic stage at diagnosis, *N* (%)		
M1	6 (46)	37 (32)
Presence of bone metastasis, *N* (%)		
Bone only	3 (23)	34 (30)
With visceral metastasis (lung, liver)	4 (31)	22 (19)
Presence of lung metastasis only, *N* (%)	2 (15)	4 (3)
Presence of liver metastasis, *N* (%)	2 (15)	10 (9)
Use of standard ADT, *N* (%)	13 (100)	114 (100)
Use of abiraterone, *N* (%)	3 (23)	47 (41)
Use of enzalutamide, *N* (%)	5 (38)	28 (25)
Use of docetaxel, *N* (%)	2 (15)	38 (33)
Use of PD-1 inhibitor, *N* (%)	4 (31)	2 (2)
PSA at diagnosis (ng/ml)		
Median (Q1–Q3)	10 (5.4–43)	13 (5.5–32)

ADT = androgen deprivation therapy; MMR = mismatch repair; PSA = prostate-specific antigen.
For comparison, we also include baseline characteristics for a group of 114 MMR-proficient men from our somatic sequencing database with full clinical and outcome data.

PSA response (median PSA reduction, 56%), with a median PSA-PFS of 7 (95% CI 3–9) mo and a median PFS of 9 (95% CI 4–11) mo. Three of these patients (75% [#8, #9, and #10]) also achieved an objective soft-tissue response lasting for 3–9+ months.

Mismatch repair-deficient prostate cancers are rare, representing <5% of tumors [2,3], but their detection has therapeutic implications [1,3,6]. We report the first case series of MMR-mutated prostate cancers by intersecting data from our institutional genomic and clinical databases. As exemplified here and in our prior studies, diagnosis of dMMR prostate cancers can be challenging because: (1) not all MMR mutations (even those predicted to be inactivating [frameshift, nonsense, and splicing lesions]) result in MMR protein loss or microsatellite instability [10], (2) the five NIH-defined microsatellite loci may be inadequate in detecting true microsatellite instability in prostate cancer and a more expanded microsatellite panel might increase sensitivity [11], (3) not all inactivating MMR gene mutations (especially structural rearrangements) can be detected by clinical-grade targeted-exon sequencing [5,12], and (4) not all dMMR prostate cancers demonstrate hypermutation or dense CD8 T-cell infiltrates [5,10]. Importantly, particular tumor grades (grade group 5, primary pattern 5) [10] or variant histologies (intraductal/ductal carcinoma and small cell carcinoma) [5,8,10] may enrich for MMR alterations.

Clinically, we have shown that dMMR prostate cancers may demonstrate remarkable sensitivity to standard ADT as well as novel hormonal agents, despite a high prevalence of *TP53* mutations [13]. PSA responses as well as median duration of responses to both conventional ADT and first-line abiraterone/enzalutamide far exceeded historical estimates [14], and were greater than those seen in our MMR-proficient population. These data raise the question of whether hormonal therapies may be immunomodulatory, potentially contributing to their efficacy in the context of dMMR prostate cancer [15]. Conversely, responses to docetaxel appeared modest, although interpretations are limited by the very small number of

Table 2 – Clinicopathological and molecular characteristics of prostate cancer patients with pathogenic MMR gene mutations

Patient ID	Gleason score, tumor stage	Specimen type tested	Variant histology	MMR gene mutation	Protein IHC status	MSI markers shifted [a]	MSI status [a]	Mutation load	Other mutations of interest
#1	4 + 5 = 9 T3a N0	RP	None noted	*MSH2* (C778X*)	MSH2 and MSH6 loss [b] MLH1 and PMS2 intact	0/5	MSS	11 muts/Mb [c]	*AKT1* (E17K) *CTNNB1* (D32G) *TMPRSS2–ERG* fusion
#2	3 + 4 = 7 T3bN1	RP	None noted	*PMS2* (L729Qfs*6)	MSH2, MSH6, MLH1, PMS2 all intact	0/5	MSS	3 muts/Mb	*TP53* (R273H) *PMS2* (T728A)
#3	3 + 4 = 7 T3b N0	RP	None noted	g*MSH6* (A1320Sfs*5)	Adequate tissue not available	No somatic (tumor) DNA analysis was performed			
#4	5 + 5 = 10	Bx	None noted	*MSH6* (F1088Sfs*2)	MSH6 loss only MSH2, MLH1, PMS2 intact	3/5	MSI-high	18 muts/Mb	*PMS2* (D414Tfs*34) *JAK1* (N339Ifs*3) *RET* (L1048Sfs*61) *RNF43* (G659Vfs*41)
#5	4 + 5 = 9	Bx	None noted	*MSH6* (F1088Lfs*5)	MSH2 and MSH6 loss MLH1 and PMS2 intact	3/5	MSI-high	35 muts/Mb	*BRCA2* (N1784Kfs*3) *HRAS* (P167Rfs*51) *JAK2* (N457Mfs*22) *TP53* (D281N)
#6	4 + 5 = 9	Bx	Intraductal carcinoma	g*MSH6* (V1192Lfs*3)	Adequate tissue not available	No somatic (tumor) DNA analysis was performed			
#7	4 + 5 = 9 T3b N0	RP	None noted	*PMS2* (M622Efs*5)	MSH2, MSH6, MLH1, PMS2 all intact	0/5	MSS	6 muts/Mb	*KMT2A* (S774Vfs*12) *TP53* (H179Q)
#8	4 + 5 = 9 T3a N0	RP	None noted	*MLH1* (heterozygous gene deletion)	MLH1 and PMS2 loss MSH2 and MSH6 intact	2/5	MSI-high	13 muts/Mb	*PTEN* (K267Efs*9) *RNF43* (G659Vfs*41) *TP53* (T155I) *TMPRSS2–ERG* fusion
#9	Unknown (no primary tumor biopsy)	Lymph node	None noted	*MSH2* (L376Ffs*13)	MSH2 and MSH6 loss MLH1 and PMS2 intact	4/5	MSI-high	42 muts/Mb	*PMS1* (T256Hfs*2) *TP53* (Q167X*) *TP53* (S240G) *PIK3CA* (H1047R)
#10	4 + 5 = 9	Bx	Intraductal carcinoma	*MSH6* (E192X*)	Adequate tissue not available	1/5	MSI-low	8 muts/Mb	*TP53* (E271V) *BRCA2* (P3189H)
#11	4 + 5 = 9	Bx	None noted	*MLH1* (T206Mfs*23)	PMS2 loss only MLH1, MSH2, MSH6 intact	2/5	MSI-high	20 muts/Mb	*BRCA1* (Q1111Efs*5) *PTEN* (T319Ifs*1) *RNF43* (G659Vfs*41) *CTNNB1* (T41A) *TMPRSS2–ERG* fusion
#12	4 + 4 = 8	Bx	None noted	g*MSH6* (E230Sfs*4)	MSH6 loss only MSH2, MLH1, and PMS2 all intact	2/5	MSI-high	22 muts/Mb	*TP53* (A76Vfs*55) *TMPRSS2–ERG* fusion
#13	4 + 5 = 9 T3a N0	RP	Intraductal carcinoma	*MSH2* (E809X*) + LOH of 2nd allele	MSH2 and MSH6 loss MLH1 and PMS2 intact	4/5	MSI-high	165 muts/Mb	*MSH6* (F1104Lfs*11) *ATM* (L663Ffs*2) *ERCC4* (M361Nfs*4) *ERCC5* (E474Nfs*15) *FANCM* (V1336Lfs*2)

Bx = prostate biopsy; g = germline mutation; IHC = immunohistochemistry; LOH = loss of heterozygosity; MMR = mismatch repair; MSI = microsatellite instability; MSS = microsatellite stable; muts = mutations; RP = radical prostatectomy.

[a] MSI status was determined from targeted next-generation DNA sequencing (Personal Genome Diagnostics, Baltimore, MD, USA) using the five well-characterized NIH-defined mononucleotide sequences (BAT-25, BAT-26, NR-21, NR-24, and MONO-27), as previously described [7]. MSI-high status is defined by shifts in two to five markers, MSI-low status is defined by a shift in one marker, and MSS status is defined by no shifted markers.

[b] In cases of protein loss by IHC, the loss was typically homogeneous rather than focal for all of the MMR proteins assayed.

[c] Tumors with mutational loads of ≥10 mutations/Mb were considered hypermutated. Eight of eleven evaluable cases (73%) exhibited hypermutated tumors.

taxane-treated patients. Finally, while anecdotal PSA and objective responses were observed using PD-1 inhibitors, durability of such responses (median, 9 mo) could be improved by using these agents earlier or in combination with other immunological or standard therapies [1]. Our conclusions are limited by the small cohort size and the retrospective nature of this analysis, and should be interpreted with extreme caution.

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Study concept and design: Antonarakis, Lotan.
Acquisition of data: Antonarakis, Shaukat, Isaacsson Velho, Kaur, Shenderov, Pardoll, Lotan.
Analysis and interpretation of data: Antonarakis, Shaukat, Isaacsson Velho, Kaur, Shenderov, Pardoll, Lotan.
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