Review Article

Management of metastatic castration-resistant prostate cancer in Middle East African countries: Challenges and strategic recommendations

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Abstract

Despite the reliance on Western guidelines for managing prostate cancer (PC), there are wide variations and gaps in treatment among developing countries such as the Middle East African (MEA) region. A multidisciplinary team of experts from the MEA region engaged in a comprehensive discussion to identify the real-world challenges in diagnostics and treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC) and provided insights on the urgent unmet needs. We present a consensus document on the region-specific barriers, key priority areas and strategic recommendations by experts for optimizing management of mCRPC in the MEA. Limited access to genetic testing and economic constraints were highlighted as major concerns in the MEA. As the therapeutic landscape continues to expand, treatment selection for mCRPC needs to be increasingly personalized. Enhanced genetic testing and judicious utilization of newer therapies like olaparib, articulated by reimbursement support, should be made accessible for the underserved populations in the MEA. Increasing awareness on testing through educational activities catalyzed by digital technologies can play a central role in overcoming barriers to patient care in the MEA region. The involvement of multidisciplinary teams can bridge the treatment gaps, facilitating holistic and optimal management of mCRPC. Region-specific guidelines can help health-care workers navigate challenges and deliver personalized management through collaborative efforts – thus curb health-care variations and drive consistency. Development of region-specific scalable guidelines for genetic testing and treatment of mCRPC, factoring in the trade-off for access, availability, and affordability, is crucial.

Keywords: Genetic testing, metastatic castration-resistant prostate cancer, Middle East African region, multidisciplinary care

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INTRODUCTION

Prostate cancer (PC), the fifth-leading cause of mortality worldwide, is a heterogeneous disease with an indolent course of progression.[1] Over the past few years, the

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landscape of PC care has undergone dynamic changes due to evolving diagnostic approaches and novel therapies. Although most developing countries lean on Western guidelines for the management of PC, there are wide differences in practice patterns, resulting in treatment gaps. To identify the current challenges in diagnostics and treatment of metastatic castration-resistant prostate cancer (mCRPC) in the Middle East African (MEA) region, a multidisciplinary meeting with experts from different counties across the MEA region was convened. The panel aimed to gain insights on the real-world treatment practices in the MEA region in the mCRPC domain, to view them in the light of international guidelines and unify best practices across MEA. The panel deliberated on the region-specific priority needs and provided strategic recommendations for optimizing PC management through collaborative efforts.

CONSENSUS METHODOLOGY

The steering committee meeting held on December 12, 2020 included a multidisciplinary panel of eight members with a broad range of expertise in the diagnosis and management of PC across the MEA region (Saudi Arabia [*n* = two], Egypt [*n* = two], Morocco [*n* = one], United Arab Emirates [*n* = one], Lebanon [*n* = one], and Turkey [*n* = one]) [Figure 1].

Key areas including current practices for managing mCRPC, implications of genomic analysis and communicating its importance to urologists, perspectives on multidisciplinary care, and strategic recommendations for improving management were discussed in moderator-led sessions. The members provided insights on the real-world challenges in their region and provided recommendations on ways to overcome the limitations for improving PC care based on their discretion and experience. The meeting concluded with the prioritization of urgent unmet needs and actionable elements to improve patient outcomes in the MEA region. The opinions and responses of the expert committee were assimilated and a thematic qualitative analysis was conducted to systematically categorize the region-specific recommendations and action plans.

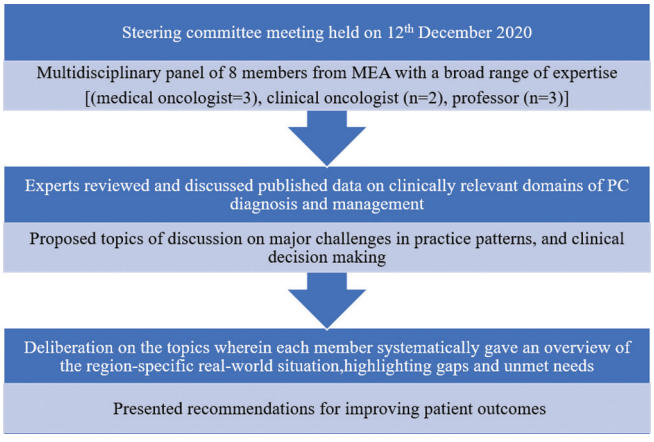

Figure 1: Flowchart depicting the process of steering committee meeting for consensus development

BURDEN AND EPIDEMIOLOGY IN MIDDLE EAST AFRICAN

Globally, PC has an age-standardized incidence (ASIR) (per 100,000) and mortality rates (per 100,000) of 30.7 and 7.7, respectively.[1] PC is one of the most common cancers in the MEA region. ASIR of PC is lower in the Arab countries compared to North American and European regions; however, it is rising steadily[2,3] [Table 1].[1] A study from a tertiary referral center in Lebanon reported that 22.6% of the patients presented with advanced stage 4 disease at diagnosis.[4] Late-stage PC has poor survival outcomes, with the American Cancer Society estimating a 5-year relative survival rate of 30% for distant PC.[5]

Herein, we present the challenges, recommendations, importance of multidisciplinary care and the way forward in diagnosis and management of PC in the MEA region.

CURRENT CHALLENGES AND RECOMMENDATIONS FOR PROSTATE CANCER DIAGNOSIS IN MIDDLE EAST AFRICAN

Although most experts reported wide availability of diagnostic approaches such as prostate-specific membrane antigen-positron emission tomography with computerized tomography (PSMA-PET-CT scan), their scarcity was highlighted in Saudi Arabia and Morocco [Table 2]. All the experts (except Saudi Arabia) reported conducting BRCA and homologous recombination repair (HRR) testing in an mCRPC setting; however, lack of insurance cover was an important

Table 1: Age-standardized incidence and mortality rates of prostate cancer

Country	ASIR (per 100,000)	ASMR (per 100,000)
Morocco	23.6	11.8
United Arab Emirates	13.4	3.4
Turkey	42.5	11.3
Lebanon	28.5	9.7
Egypt	13.9	7.9
Saudi Arabia	7	2.5
United States	72.0	8.2
United Kingdom	77.9	12.4

Prostate Globocan factsheet 2020. Available from https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf. Accessed Jan 2021. ASIR: Age-standardized incidence rate, ASMR: Age-standardized mortality rates

Table 2: Challenges and recommendations for diagnosis and genetic testing of prostate cancer in Middle East Africa

	Availability and adequate timing of genomic testing	Challenges	Recommendations
Egypt	Testing for BRCA essential and available, however testing needed for somatic as well as germline mutations Timing for testing is crucial; testing in early disease stage might be better	Tissue suitability: Concern over availability of suitable tissue at early stages of disease, after prolonged ADT and re-biopsy in irradiated prostate. In addition, tissue may not be available in case of prostatectomy Special preparation of bone in case of bone biopsy Reimbursement: BRCA not reimbursed by the government	For generalized genomic profiling, preferable to have recent biopsy, as quality of DNA can degrade over time Liquid test can be used for BRCA, in future to evaluate discordance between blood test and somatic test from tumor tissue Streamlined approach for genetic testing in the urology clinic
Lebanon	Access to genetic testing for BRCA and HRD crucial Next generation genetic sequencing available Testing at an early stage might be useful	Long duration for obtaining results Concern over the type of genetic testing to be evaluated Bone metastasis testing difficult owing to complex bone preparation Reimbursement: Testing not reimbursed by social security, government or private insurance	Need refined definitive guideline Imperative to sensitize urologist for genetic testing early in the disease Need virtual molecular biology board for interpretation of results
Morocco	DNA alterations, BRCA testing performed in castration phase	PSMA PET not available BRCA mutation testing not reimbursed and not performed in all public hospitals Long time lag to obtain results, thus delaying treatment Due to tumor instability, DNA alterations may change over time with metastatic disease progression Ethnic variations	Essential to understand the type of DNA alterations to be evaluated - for germline and somatic mutations BRCA testing is crucial. Although general genomic profiling may not be essential, MSI may be required Urologists need better access to reliable results and interpretation. Crucial to support urologists for genetic testing for BRCA mutation In addition, differences in ethnicity need to be considered Virtual genetic counseling clinics are needed
Turkey	BRCA and MSI test are reimbursed for all patients with prostate cancer, however they are not widely available in common practice yet Testing conducted at onset of castration resistant prostate cancer. However, conducting it earlier would be beneficial	Long duration for obtaining results for BRCA testing Currently, BRCA testing can't be validated Region-specific testing algorithm not available, mostly international guidelines followed	Need of MDT Need reflex genetic testing from pathology to molecular labs Need virtual genetic counseling clinics
UAE	BRCA and HRR testing used in mCRPC setting	Although BRCA and HRR testing used in the mCRPC setting, concern over long time for obtaining results and cost May lead to patient anxiety Region-specific testing algorithm not available Though biopsied tissue is preserved optimally, patient mobilization to international places may lead to scarcity of detailed report	Genomic profiling is essential for prognosis and to optimize the treatment at diagnosis of CRPC or at failure of first-line therapy Genomically driven trials with better companion diagnostics will help in advancing precision medicine Genomic profile summary predicting response to ADT, sensitivity to chemotherapy, and neuroendocrine differentiation can help identify the best therapy and sequence for the patient Optimal timing at mCRPC stage is crucial Need virtual genetic counseling clinics
Saudi Arabia	Only few centers, tertiary care facilities offer HRD testing	Government centers do not perform PSMA Limited availability of PSMA PET and HRD testing	No comments

ADT: Androgen deprivation therapy, BRCA: Breast cancer gene, HRD: Homologous repair deficiency, PC: Prostate cancer, HRR: Homologous recombination repair, mCRPC: Metastatic castration-resistant PC, MDT: Multidisciplinary team, MSI: Microsatellite instability, PSMA PET: Prostate-specific membrane antigen-positron emission tomography with computerized tomography

barrier for genetic testing. In addition, a long time lag for obtaining results may lead to delayed treatment and poor outcomes. The experts raised concern regarding the lack of refined definitive guidelines for the type of genetic testing and the absence of region-specific testing algorithm. Tissue suitability for testing was another area of concern, with a lack of guidance to determine the criteria for tissue and bone biopsy. With the progressive decline in prostate activity, the volume of viable cells would be minimal, especially if patients had received radical radiotherapy previously. Availability of suitable tissue at early stages of the disease, after prolonged androgen deprivation therapy (ADT) and in case of prostatectomy were considered challenging areas. The experts discussed difficulties in bone metastasis testing, owing to the complexities for bone preparation. The

effect of bone-targeted agents on biopsy and the problem of calcifications while bone testing, especially if the patient received bone-targeted agents previously, need to be explored further. Regarding tissue preservation and archiving optimization, the experts deliberated that though biopsied tissues were preserved optimally, the mobilization of patients to international places led to scarcity of detailed reporting.

Genomic profiling is pivotal for upfront prognosis and treatment optimization – highlighting the need for a streamlined roadmap and more refined definitive guideline for genetic testing [Table 2]. Genomically driven trials with better companion diagnostics for advancing precision medicine and genomic profile summary predicting response to ADT, sensitivity to chemotherapy, and neuroendocrine differentiation can help identify best therapy and sequence for the patient. Optimal timing at the mCRPC stage was also deemed as a crucial aspect. Although testing is usually conducted at the onset of castration-resistant PC, the experts opined that conducting the tests at an early stage might be useful. As PC evolves over a longer period (except a small proportion of patients who develop rapidly), the experts concurred for conducting a new biopsy when patients develop metastatic disease. Furthermore, in the case of generalized genomic profiling, the experts recommended conducting a recent biopsy, as the quality of DNA may degrade over time. The PROFOUND and PROPEL trials had no time limitation for the next-generation sequencing test and used archived issues.[6,7] Liquid biopsy can be used for BRCA testing in future as it will be helpful to evaluate discordance between blood tests and somatic tests from tumor tissue. It is imperative to sensitize urologists for genetic testing early in the disease and provide them enhanced access to reliable results and interpretation. Virtual molecular biology board, multidisciplinary panels for interpretation of results from genetic testing, and formulation of genetic counseling clinics are critical.

EVIDENCE SUPPORTING THE STRATEGIC RECOMMENDATIONS

Overview of molecular landscape in Metastatic Castration-Resistant Prostate Cancer

The molecular profile of mCRPC is highly heterogeneous, encompassing different germline and somatic genetic alterations such as homologous repair deficiency (HRD) (e.g., BRCA1, BRCA2, ataxia telangiectasia mutated (ATM), BRIP1, CHEK2, NBN, BARD1, RAD51C, MRE11A, and PALB2), mismatch repair (MMR) deficiency (e.g., MLH1, MSH2, MSH6, and PMS2) and microsatellite instability (MSI).[8,9] The DNA damage response (DDR), an essential pathway for survival of normal and malignant prostate cells, includes crucial genes, such as breast cancer susceptibility gene (BRCA) 1/2, ATM and partner and localizer of BRCA2 (PALB2). A study identified common deleterious DNA-repair gene mutations in 16 genes, including BRCA2 (5.3%), ATM (1.6%), CHEK2 (1.9%), BRCA1 (0.9%), RAD51D (0.4%), and PALB2 (0.4%).[10] A systematic review showed that the prevalence of DDR germline and/or somatic mutations (among unselected patients) was 22.67% in mCRPC, with BRCA2 having the highest mutation rate – warranting testing of all patients with metastatic disease and not just those with the familial disease.[11] Poly (ADP)-ribose polymerase inhibitors (PARPi) inhibit DNA repair pathways and cause apoptosis of cancer cells, especially in HR-deficient cells.[12] PARPi have emerged as a therapeutic approach to target the DDR pathway harboring genetic mutations (e.g., BRCA1/2 mutations). Many ongoing clinical trials are exploring the benefit of PARPi alongside other targeted therapeutic agents such as pembrolizumab for mutations in the HRD or MMR genes. The FDA has approved two PARPi, olaparib and rucaparib for BRCA-mutated mCRPC.[13,14] Recent guidelines have recommended olaparib and rucaparib for patients with deleterious germline or somatic HRR gene-mutated mCRPC. Pembrolizumab was approved by the FDA in 2017 and is recommended for the treatment of all solid tumors, including PC that have mutations in MMR genes and or MSI in the tumor.[15] Given the high proportion of patients with actionable mutations and the evolution of novel therapies, genetic testing is now an important standard of care. Guidelines such as the National Comprehensive Cancer Network (NCCN) have reflected on the importance of DDR mutation testing in mCRPC and have recommended germline genetic testing for patients with high-risk or metastatic disease or family history of known germline DNA repair gene abnormalities (especially BRCA2 mutation) – for obtaining clarity on prognosis, therapeutic choices, in addition to informing the patient about personal and familial risk.[16,17]

The Germline Genetics Working Group (GGWG) described that integrating genetic testing into oncology and urology clinical scenarios is challenging due to the increased burden of patients requiring testing and the limited access to genetics providers.[18] It is crucial to have trained genetic providers to assess genetic risk, order appropriate testing, and interpret test results; however, majority of the workforce are centered in urban areas

and academic institutions. Due to the scarce availability of such specialists, it is prudent that other health care providers such as oncologists, urologists, and primary care physicians are sufficiently trained in the area of molecular genetics. A survey of U.S. (n = 132) urologists revealed that only 12% perform germline testing, 44% refer to a genetic counselor, 11% do both, and 33% do not test/refer. The survey highlighted that only 4% had formal education in genetics, but specializing in PC/oncology was significantly associated with recommending germline testing (P = 0.0009).[19] Similarly, a provider survey from Birmingham showed that only 39% of eligible patients were referred, while testing was completed in 11%. About 70% of respondents cited that lack of genetics workforce and lack of knowledge (60%) were barriers to genetic testing.[20] The 2019 Philadelphia Prostate Cancer Consensus advocated the utilization of digital health technologies such as phones and video telemedicine for facilitating access. It also recommends using hybrid service models encompassing balanced responsibilities between physicians and geneticists, alongside multidisciplinary collaboration between geneticists and clinicians to determine the best approach.[21]

The selection of appropriate patients for testing is critical. NCCN and other consensus guidelines elucidate key criteria such as metastatic disease or strong family history to screen and identify patients.[16-21] GGWG suggests that patient-completed family history questionnaires or automated electronic medical records can facilitate referral and testing processes. Insurance and out-of-pocket cost for patients are crucial elements for propagating genetic testing. The Philadelphia consensus outlined that targeted testing for selected individuals might be beneficial in this regard.[21] Complete and detailed family histories can ensure that the most informative, cost-effective testing is performed; however, it may be prudent to include other associated genetic tests as well. The NCCN guidelines recommend considering BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, and PMS2 for testing; however, the Philadelphia consensus included HOXB13 and DNA MMR genes.[16-21] GGWG recommends that factors such as insurance networks, laboratory billing practices, follow-up testing options for family members, turnaround times, and availability of genetic counseling services are deciding factors for genetic testing. Evidence has shown low awareness and knowledge of genetic counseling, and testing for cancer susceptibility among ethnic minority groups and socioeconomically disadvantaged individuals may result in anxiety. Considering the evolving therapeutic landscape of PC, it is essential to make strategies for minimizing disparities for optimizing treatment and improving outcomes.[22] Increased awareness for genetic testing through counseling for PC, involving shared decision making between provider and patient; discussion of benefits, risks, financial implications; and genetic discrimination laws are important.[21]

MANAGEMENT OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER

Overview of international guidelines for the management

Recent guidelines have recommended novel agents such as olaparib for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC after prior anti-androgen therapy (enzalutamide or abiraterone)[16,23,24] [Table 3]. A summary of ongoing or completed trials of novel therapies for mCRPC is presented in Table 4.[6,25-30]

Current treatment practices for Metastatic Castration-Resistant Prostate Cancer in Middle East African region and their comparison with the Western world

A real-world study from the U. S. reported that abiraterone/prednisone accounted for 65% of first-line, enzalutamide for 54% of second-line therapies, and docetaxel 24% of third-line therapy; the median overall survival was longer in patients who received abiraterone/prednisone, enzalutamide, and docetaxel therapies (23.7 months) than those who did not (10.1 months).[31] PROXIMA (Treatment Patterns in Patients with Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) a multicenter, prospective registry including patients from Asia, Europe, Latin America, and MEA highlighted regional influences, with chemotherapy being more frequently prescribed in MEA countries (52.3%) compared to Europe (27.1%) – attributed to the unavailability of other agents in these countries. The study showed that median overall survival for all patients was 15.1 months (95% confidence interval, 14.0–17.6).[32] ASPIRE-PCa, a global study including patients from the Middle East and North Africa in late-stage PC reported ADT as the treatment of choice, gonadotropin-releasing hormone agonist with anti-androgen for flare protection only was the most selected ADT (leuprolide [48%]; bicalutamide [48%] and abiraterone [8%] were most common, while enzalutamide was less frequently chosen [3%]).[33] The APCCC Satellite Meeting for the Middle East presented resource-stratified consensus recommendations for the management of patients with high-risk and advanced PC[34] [Table 5].

Table 3: Summary of major recommendations for the management of metastatic castration-resistant prostate cancer

International guidelines[16,23]	No prior docetaxel/no prior novel hormone therapy: Preferred: Abiraterone, docetaxel, enzalutamide In certain circumstances: Sipuleucel-T, radium-223 (symptomatic bone metastasis) Other secondary hormone therapy Prior novel hormone therapy/no prior docetaxel: Preferred regimens: Docetaxel, Sipuleucel-T In certain circumstances: Olaparib (HRRm), cabazitaxel/carboplatin, pembrolizumab (MSI-H/dMMR), radium-223, rucaparib (BRCAm) Other: Abiraterone, abiraterone+dexamethasone, enzalutamide, other secondary hormone therapy Prior docetaxel/no prior novel hormone therapy: Preferred: Abiraterone, cabazitaxel, enzalutamide In certain circumstances: Mitoxantrone for palliative therapy, cabazitaxel/carboplatin, radium-223, pembrolizumab (MSI-H/dMMR) Other: Sipuleucel-T, other secondary hormone therapy Prior docetaxel and prior novel hormone therapy Preferred regimens: Cabazitaxel, docetaxel In certain circumstances: Olaparib (HRRm), cabazitaxel/carboplatin, radium-223, pembrolizumab (MSI-H/dMMR), Mitoxantrone, rucaparib (BRCAm) Other: Abiraterone, enzalutamide, other secondary hormone therapy
Regional guidelines[24]	Patients who did not receive chemohormonal therapy: For symptomatic patients and rapidly progressing disease: Docetaxel with prednisone For patients with no or mild symptoms and no visceral metastases: Abiraterone and prednisone For patients with no or mild symptoms: Enzalutamide For patients with only symptomatic bone metastases: Radium223 Progressed on or after docetaxel: Cabazitaxel with prednisone, abiraterone with prednisone, enzalutamide, and radium223 Patients with CRPC should continue ADT indefinitely

NCCN Clinical Practice Guidelines in Oncology for Prostate Cancer, Version 1.2021; AUA/ASTRO/SUO, AUA/ASTRO/SUO 2020; Saudi Oncology Society and Saudi Urology Association clinical management guidelines 2017. ADT: Androgen deprivation therapy, HRRm: Homologous recombination repair mutation, MSI: Microsatellite instability, MMR: Mismatch repair, BRCA: Breast cancer gene, PC: Prostate cancer, CRPC: Castration-resistant PC, AUA: American Urological Association, ASTRO: American Society for Radiation Oncology, SUO: Society of Urologic Oncology, NCCN: National Comprehensive Cancer Network

Table 4: Summary of key ongoing or completed trials of novel therapies for metastatic castration-resistant prostate cancer

PARPi	Name of study	Population	Outcomes	Result
Olaparib	TOPARP-B[25]	mCRPC, HRD selected, previously given taxane	Composite RR (PSA decline by≥50%, objective tumor response, CTC reduction)	Composite RR 54% at 400 mg dose and 39% for 300 mg dose
	PROfound[6]	mCRPC, HRD selected, given second-generation hormonal agent and one taxane	Primary outcome: rPFS in cohort A Secondary outcome: rPFS in cohort A+B OS: cohort A	rPFS cohort A versus control 7.4 versus 3.6 months rPFS cohort A+B versus control 5.8 versus 3.5 months OS cohort A versus control 18.5 versus 15.1 months
Rucaparib	TRITON2[26,27]	mCRPC, HRD selected, given second-generation hormone agent and taxane	ORR (RECIST/PCWG3) Secondary: PSA decline by≥50%	ORR-BRCA1/2: 43.5-50.8% PSA-BRCA1/2 mutation: 53.8% ORR for other HRD mutation: 28.6%
Niraparib	GALAHAD[28]	mCRPC, HRD selected, given second-generation hormone agent and taxane	ORR (RECIST) Composite RR (PSA decline by≥50%, objective tumor response, CTC reduction)	ORR for BRCA/2 mutation 41% Composite RR for BRCA1/2 mutation 63%
Pembrolizumab	KEYNOTE-199[29]	Cohorts 1 and 2: RECIST measurable PD-L1-positive and PD-L1-negative disease, Cohort 3: Bone predominant disease	ORR by RECIST Disease control rate OS	ORR 5% in cohort 1 and 3% in cohort 2 Disease control rate: 10% in cohort 1, 9% in cohort 2, and 22% in cohort 3 Median OS: 9.5 months in cohort 1, 7.9 months in cohort 2, 14.1 months in cohort 3
Lutetium-PSMA-617	LuPSMA trial Phase II[30]	Progressive disease per RECIST or bone scan after standard treatments, with taxane and second-generation anti-androgens	PSA response (≥50% decline from baseline)	17 (57%) of 30 patients (95% CI 37-75) achieved a PSA decline of 50% or more

PARPi: Poly (ADP-ribose) polymerase inhibitors, mCRPC: Metastatic castration-resistant prostate cancer, RR: Response rate, HRD: Homologous recombination deficiency, CTC: Circulating tumor cells, rPFS: Radiographic progression-free survival, OS: Overall survival, ORR: Objective response rate, RECIST: Response evaluation criteria in solid tumor, BRCA: Breast cancer, PSMA: Prostate-specific membrane antigen, PD-L1: Programmed death-ligand 1, PSA: Prostate-specific antigen

Table 5: Current treatment practices for metastatic castration-resistant prostate cancer in the middle East African region and their comparison with the western world

	US[31]	APCCC Satellite Meeting for Middle East[34]	PROXIMA registry[32]
First-line	(*n*=1980) Abiraterone (37%) Enzalutamide (28%) Docetaxel (15%) Sipuleucel-T (7%) Radium-223 (2%) Cabazitaxel (1%) Combination therapy, including radium-223 (7%)	Asymptomatic/minimally symptomatic men who did NOT receive Docetaxel in the castration-sensitive setting: Abiraterone or Enzalutamide: (87%) Symptomatic men who did receive Docetaxel in castration-sensitive setting: Abiraterone or Enzalutamide: (86%)	First subsequent treatment: Chemotherapy (38.3%); the most frequent were taxanes (26.4%) Hormonal therapy (57.5%); the most frequent were CYP-17 inhibitors (27.4%), antiandrogen agents (14.6%), glucocorticoids (13.7%), and receptor blockage antiandrogen agents (11.8%) Immunotherapy (0.9%)
Second-line	(*n*=969) Enzalutamide (34%) Abiraterone (20%) Docetaxel (14%) Cabazitaxel (6%) Radium-223 (3%) Sipuleucel-T (2%) Combination therapy, including radium-223 (17%)	Progressive disease to first-line Abiraterone or Enzalutamide: Taxane (85%) Symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression) after use of first-line Abiraterone or Enzalutamide: Taxane (100%)	Second subsequent treatments: Chemotherapy (44.8% with 28.8% only chemotherapy) Hormonal therapies (44.4% with 18.8% receiving only hormonal therapy) Palliative radiotherapy (8.7%) Targeted therapies (6.3%, with 4.5% receiving only targeted therapy) Corticosteroids (6.3%) Immunotherapy (0.7%)
Third-line	(*n*=414) Docetaxel (24%) Enzalutamide (16%) Abiraterone (14%) Cabazitaxel (11%) Radium-223 (8%) Sipuleucel-T (3%) Combination therapy, including radium-223 (18%)	mCRPC progressing on or after second-line Docetaxel for mCRPC and prior treatment with Abiraterone/Enzalutamide: Cabazitaxel (81%)	Third subsequent treatments: Hormonal therapies (50.6%, with 25.9% only hormonal therapies) Chemotherapy (32.1%, with 21.0% only chemotherapy) Palliative radiotherapy (18.5%) Targeted therapies (7.4%, with 4.9% receiving only targeted therapy)

PC: Prostate cancer, mCRPC: Metastatic castration-resistant PC, PROXIMA: Prospective registry mCRPC previously treated with docetaxel-based chemotherapy

CURRENT CHALLENGES AND RECOMMENDATIONS IN TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IN MIDDLE EAST AFRICA

Gaps in treatment of Metastatic Castration-Resistant Prostate Cancer

Most experts concurred regarding the availability of major therapeutic agents such as enzalutamide, abiraterone, Lutetium 177 PSMA radionuclide therapy; however, deficiencies were highlighted in Morocco and Saudi Arabia. All the experts reported the unavailability of radium 223 as a therapeutic agent. There were congruent views regarding the lack of robust data from prospective studies for treatment sequencing and lack of data on combination therapy for mCRPC reporting better survival outcomes. Majority of the experts reported the absence of region-specific national guidelines for PC, except Lebanon, where guidelines though available, were not updated. The panel unanimously agreed on primarily using international guidelines like NCCN due to the absence of region-specific national guidelines; however, the experts added that formulation of national guidelines is anticipated in Turkey, Egypt, and Morocco in the near future. Another major area of concern was the lack of reimbursement of therapeutics, especially novel agents such as olaparib. The unavailability of PARPi in government centers was reported as a deficiency in countries such as Saudi Arabia.

Recommendations for Metastatic Castration-Resistant Prostate Cancer treatment

All the experts concurred on building a multidisciplinary collaboration for guideline creation and regular upgradation. The experts elaborated the need for a committee to support continuity and suggested empowering skilled clinicians from private sectors through incentives for regular implementation. The experts discussed the need of a dedicated team, including skilled urologist, oncologist, radiation oncologist, medical oncologist, pathologist, nurse and data management personnel. Emphasis was also laid on understanding the importance of real-world management practices alongside scientific recommendations. Conducting meeting of key opinion leaders, including representatives from government and payers, to facilitate region-specific personalization of guidelines might facilitate access. Easily comprehensible procedures funded by the government were regarded as the pathway for the distribution of new national guidelines to practicing clinicians.

EVIDENCE SUPPORTING THE STRATEGIC RECOMMENDATIONS

Role of multidisciplinary care for Metastatic Castration-Resistant Prostate Cancer management

The experts unanimously concurred regarding the utilization of MDT for optimized PC care and management. Traditional care in PC management carries disadvantages such as

fragmented care, lack of prospective treatment sequencing, rapidly evolving treatment options, and delayed care. Given the complexities of multimodal treatment for patients with PC, the use of multidisciplinary teams can aid the formulation of optimal treatment strategies for individual patients. Different stakeholders in the MDT may include urologist, radiation oncologist, medical oncologist, pathologist, imaging specialist, nurse and data management professional in the core team; medical physicist, palliative care specialist, psychologist, genetic counselor, patient advocate, and clinical trial coordinator in the noncore team. In addition, support services and navigators also play an important role [Figure 2]. MDT approach guarantees a higher probability for the patient to receive adequate information on the disease and on all possible therapeutic strategies, balancing advantages, and related adverse effects. A team approach to PC care can reduce mortality and improve the quality of life for the patient. A real-world study demonstrated that patients treated via the MDT survived on average 16.9 months longer than those in the matched Surveillance, Epidemiology and End Results cohort.[35] Guideline-focused care with improved diagnostic and therapeutic paths, increased patient satisfaction, decreased time from presentation to treatment, reduction in errors or variability, as well as timely access to physical and psycho-emotional rehabilitation programs have been shown to be improved by a multidisciplinary approach to PC care.[36-42]

Importance of region-specific consensus guidelines

The experts discussed the importance of region-specific national clinical guidelines to translate evidence from bench to bedside. Region-specific guidelines can help reduce health-care variation, improve consistency in care delivery across systems and countries, modify physician behavior, promote effective interventions, and discourage the use of less effective therapies. Such tailored guidelines can support advanced practice providers and less experienced trainees for the timely and precise clinical decision process, factoring in the regional challenges for access, availability, and affordability. Developing guidelines in low-income and middle-income countries should entail a strategic approach to conduct reviews, present evidence, and promote transparency of consensus-based procedures through multidisciplinary engagement from government and academia, regulators, and practitioners.[43-45] Definitive guidelines incorporating patient preferences, treatment risks, and comorbidities to guide clinicians' choices can drive personalized medicine and enhance patient care.[46]

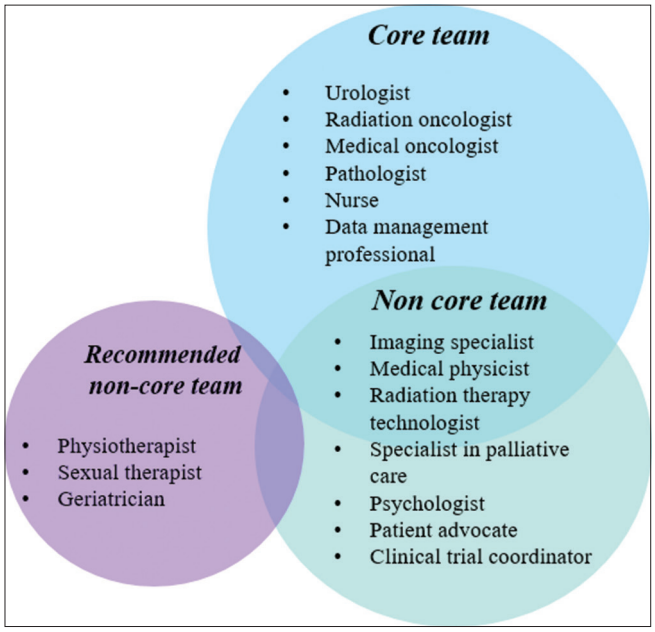

Figure 2: Multidisciplinary care for Metastatic Castration-Resistant Prostate Cancer. Footnote: Adapted from ESO task force initiative prostate cancer care units in Europe, CROH

FUTURE DIRECTIONS FOR METASTATIC CASTRATION RESISTANT PROSTATE CANCER MANAGEMENT

Defining the best sequencing and combination strategies to delay resistance, decrease toxicities, and improve survival outcomes is warranted for mCRPC. Several ongoing clinical trials are exploring this paradigm, especially in combination with recently introduced agents such as olaparib and pembrolizumab.[47-51] The challenges of tumor instability and DNA alterations over time with disease progression can be mitigated by liquid biopsies, thus developing a roadmap of personalized treatment strategies in future.[52,53] Furthermore, utilization of artificial intelligence in diagnostic and prognostic prediction to facilitate decision-making can open opportunities for personalized treatment in mCRPC.[54,55]

CONCLUSION

As the list of the therapeutic landscape of mCRPC continues to expand, treatment selection needs to be personalized through enhanced genetic testing. Multidisciplinary care, including stakeholders from different specialties, is critical to deliver optimal care. Formulation of region-specific scalable strategies and guidelines to deliver personalized genetic testing are essential to guide precision medicine and improve patient outcomes. However, insurance for genetic testing and newer therapies like olaparib is pivotal for regular implementation. Guideline sustainability and economical cost are crucial elements for influencing real-world treatment decisions in MEA. In addition, enhancing awareness regarding the need for testing through

educational activities can be pivotal for genetic care delivery. Hybrid methods for educational activities encompassing digital technologies can play a central role in overcoming barriers pertaining to access and availability of mCRPC management in MEA.

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Conflicts of interest

AA has no conflict of interest to disclose; AM received honoraria and consultation fees from AstraZeneca, and Janssen and Bayer; HM received speaker honorarium (Astellas, Pfizer, Amgen, Ipsen, MSD) and participated in advisory boards of Janssen, Amgen, Pfizer, and Astrazeneca; JA received speaker honorarium from AstraZeneca, Janssen, Astellas, and Merck; MA is a member of advisory board, consultant, and speaker for Amgen, Astellas, AstraZeneca, Hoffman la Roche, Janssen Cilag, Merck Serono, Novartis, Mundipharma, MSD, Ely Lilly, Sanofi-Genzyme, Servier, BMS, and Bayer; MG participated in advisory board meetings of Sanofi-Aventis, Jansen, Astellas, Pfizer, MSD, BMS, Roche, Lilly, Novartis, and AstraZeneca; SB received research support (Pfizer, BMS, Bayer, Sanofi), speaker honorarium (Lilly, Roche, AstraZeneca, Merck Serono, Newbridge, Janssen, BMS, Servier) and is an advisor to Roche, IPSEN, Astellas, Astrazeneca, Amgen, Bayer and Servier; YU received speaker honorarium (Amgen, Astellas, Bristol Myers-Squibb, Janssen, Merck, Novartis, Pfizer, Roche) and is advisor to Amgen, Astellas, AstraZeneca, Bristol Myers-Squibb, Janssen, Merck, Novartis, Pfizer and Roche.

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