EDITORIAL

GERMLINE GENETIC TESTING IN PROSTATE CANCER, A POTENTIAL FOR NEW UNDERSTANDING SCREENING, EVALUATION AND TREATMENT OF PROSTATE CANCER

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Germline genetic testing is revolutionizing prostate cancer (PCA) care, with studies revealing inherited mutations (pathogenic variants) in a spectrum of cancer risk genes[1]. Analyses from clinical cohorts of men with PCA have reported germline mutation rates of 15% to 17% regardless of stage, with rates of DNA repair mutations reported to be approximately 12% in men with metastatic PCA[2]. Patients with prostate cancer should now undergo genetic testing of tumor tissue to identify the 30% or so of patients who can benefit[3]. The highest level of PCA risk has been reported for mutations in BRCA2, and HOXB13, with BRCA2 mutations associated with poor outcomes[1-5].

Genetic testing for men with PCA is being driven increasingly by precision therapy and precision management considerations affecting oncology and urology. For example, olaparib was given Breakthrough Therapy designation by the US Food and Drug Administration for BRCA1/2- or ATM-positive metastatic castration-resistant prostate cancer (mCRPC) on the basis of the TOPARP-A trial demonstrating improved responses particularly in patients with DNA repair mutations[6].

Indeed, mutations in multiple genes (BRCA2, BRCA1, ATM, CHEK2, PALB2, RAD51D, NBN, MLH1, MSH2, PMS2, and MSH6) may provide clinical trial options for men with mCRPC, because genetically informed trials are expanding for PCA treatment [7].

Most experts distinguish three major types of cancer risk. General population risk describes sporadic cancers occurring by chance. In this case, affected patients test negative for any known deleterious mutations within their family, and their close relatives typically do not have the same cancer(s).

Familial cancer risk describes the risk for cancers that arises from both genetic and environmental factors. These cancers tend to cluster within families and show no specific inheritance pattern.

Hereditary cancers, mutations occur in germ cells and present in every cell in the body. Hereditary cancers occur when a parent passes an altered gene (germline mutation) to a child. Hereditary cancers are often diagnosed at an earlier age than is otherwise typical and affected patients may develop more than one type of cancer. Patients with hereditary cancer(s) often have relatives with the same or related cancers. Only about 5% to 20% of cancers are hereditary[8].

Recently, further research has implicated specific mutations in hereditary prostate cancer and has found that men with these variants are at greater risk for high-grade disease. In the Genetic Evaluation of Men study, researchers used multigene sequencing in 200 men who had prostate cancer or were at increased risk. A total of 5.5% had detectable mutations, which usually involved the DNA repair genes BRCA1, BRCA2, ATM, BRIP1, and MSH6[9].

Patients with prostate cancer should now undergo genetic testing of tumor tissue to identify the 30% or so of patients, who can benefit — as is already routinely being done for breast, ovarian and lung cancer,

The results come from the phase 3 PROfound study of the PARP inhibitor olaparib (Lynparza, AstraZeneca) in patients who tested positive for DNA repair gene alterations including BRCA1, BRCA2, or ATM mutations.

These were patients with metastatic castration-resistant prostate cancer (mCRPC) whose disease had progressed after treatment with the newer hormonal agents such as abiraterone (Zytiga, Janssen) or enzalutamide (Xtandi, Medivation and Astellas Pharma), and/or with taxane chemotherapy.

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alterations and 34% had other alterations. Between 6.6% and 8.4% of patients had more than one alteration.

At the Presidential session at ESMO 2019, Maha Hussain, MD, and colleagues presented the initial results of PROfound. Cohort A included patients with alterations in BRCA1, BRCA2 or ATM, while Cohort B patients included any one of 12 other homologous recombination repair alterations (BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D or RAD54L). Patients were randomized 2:1 to olaparib (300 mg bid) or the physician's choice of enzalutamide (160 mg/day) or abiraterone (1000 mg/day + prednisone 5mg BID). The primary endpoint was radiographic progression-free survival (rPFS) in Cohort A, assessed by blinded independent central review and analyzed via a stratified log-rank test. Crossover to olaparib was allowed after blinded independent central review progression [10].

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The name "BRCA" is an abbreviation for "BReast CAncer gene." BRCA1 and BRCA2 are two different genes that have been found to impact a person's chances of developing breast cancer. BRCA1 and BRCA2 are tumour suppressor genes and both are inherited in an autosomal dominant fashion with incomplete penetrance. Tumorigenesis in individuals with germline mutations in the BRCA genes requires somatic inactivation of the remaining wild-type allele. Both genes encode large proteins that function in multiple cellular pathways.

Men who carry the BRCA2 gene mutation, which is linked to breast and ovarian cancer, are at risk of developing aggressive prostate cancer and so should undergo regular prostate-specific antigen (PSA) testing, suggest findings from a major study.

The IMPACT Study involved almost 3000 men from 20 countries who were recruited from families known to harbor carriers of mutations of the BRCA1 and BRCA2 genes and who underwent annual PSA testing and biopsy. The results, which were published recently in European Urology, show that men who carried the BRCA2 mutations were almost twice as likely to develop prostate cancer than were noncarriers. They were also diagnosed with prostate cancer at a younger age and had more clinically significant disease[12].

Clinical implications

Platinum agents induce DNA crosslinks that are substrates for HR DNA repair, which is deficient in BRCA-mutated cells. Therefore, these tumours show high sensitivity to platinum-based chemotherapy, both in vitro[96, 97, 98] and in vivo.[99, 100, 101] Previous studies in ovarian cancer suggested that mutations in both genes were associated with similar responses to platinum-based chemotherapy.[101] Recently, Yang et al.[102] have reported a series of 316 ovarian cancer patients treated with surgery and adjuvant platinum-based chemotherapy in which BRCA2 mutations were associated with improved outcomes, while BRCA1-mutated or -hypermethylated tumours were not significantly different from BRCA wild-type cases. BRCA2 mutations were also associated with an increased rate of response to primary platinum chemotherapy.

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chemotherapy. Interestingly, an increase in genomic instability was found in BRCA2-related tumours, but not in those with BRCA1 loss, due to mutation or hyper methylation. This could indicate that BRCA2 lesions cause more substantial HR defects than BRCA1.

Gallagher et al have recently suggested that those patients with metastatic disease and BRCA mutations do not respond less to the standard chemotherapy regimen with Docetaxel plus prednisolone than PCa which are BRCA wild type[21].

It was observed that BRCA2 mutations are associated with worse outcome for all survival endpoints, except for survival from metastasis. No difference was seen between mutation carriers and non-carriers, which may be due to a more favourable response to chemotherapy treatments[22].

PARP (Poly(ADP-ribose) polymerases (PARPs) is an enzyme that produces large chains of poly(ADP-ribose) from NAD[23]PARP is involved in the repair of single-strand DNA breaks and its inhibition produces the accumulation of these lesions which may end in the arrest of the replication fork and the formation of DSBs[24]These DSB are only proficiently repaired by HR. In the absence of HR, as occurs when BRCA mutations are present, these DSBs are repaired by error-prone forms of DSB, such as non-homologous en-joining potentially resulting in accumulation of gene aberrations and loss of cell viability[25-26].

Germline mutations in the BRCA genes, mainly in BRCA2, not only increase the risk of developing PCa, but also have implications in the prognosis and management of the disease. BRCA-related PCa is usually aggressive, and radical treatments are preferred to surveillance, even for low-risk cases.

Further studies are needed to design a tailored management for these patients. An ongoing study, IMPACT, will clarify the benefits of PCa screening in this higher-risk population. Promising clinical trials are evaluating the role of PARP inhibitors in the metastatic setting, but more studies are needed to establish the role of adjuvant treatment, with PARP inhibitors and/or conventional chemotherapy.

The role of chemoprophylaxis in patients with high risk of aggressive forms of PCa also needs to be addressed. A better characterization of BRCA-related prostate tumours would help to identify sporadic cases with potential lethal forms of the disease that might benefit from the therapeutic strategies designed for BRCA-mutated tumours.

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