RESEARCH TOPIC MEM1

DRG mutations in prostate cancer: a guiding light for enhanced screening and personalised therapy

Curriculum MEM Clinical

Clinical Unit name and address
Department of Urology, Humanitas Clinical and Research Center

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Abstract
Prostate cancer (PCa) represents the most commonly diagnosed cancer in men and the second most common cause of cancer death in Western countries. It is estimated that 5-10% of PCa cases correlate with an inherited susceptibility to the disease. Mutations in DNA-repair genes (DRGs) were found in approximately 5% of localized PCa and in 12% of metastatic castration-resistant PCa. There is an unmet clinical need to identify high risk population and distinguish truly indolent localized cancers from progressive and potentially lethal disease, which will most benefit from early diagnosis and targeted therapies, in order to avoid underdiagnosis and undertreatment in such patients. We will test whether a dedicated screening in carriers of a DRG mutation can be more effective in early detection of aggressive PCa than the current approach (PSA), increasing the number of curable diseases.
Participants will be selected according to two strategies: 1) male consanguineous relatives of women with BRCA1/2+ cancer, 2) male consanguineous relatives of men with PCa positive for a mutation in a DRG. Strategy 1 will take advantage of the large cohort of breast/ovarian cancer patients referring to our Center. Strategy 2 will involve the mutational screening by targeted NGS of DRGs on biopsy/surgical specimens with histologically-confirmed PCa.
This is a monocentric, prospective study, designed to evaluate the sensitivity of a targeted screening in men at higher genetic risk for PCa because carriers of pathogenic mutations in a DNA repair gene. The study will be entirely conducted at the Istituto Clinico Humanitas throughout the collaboration of the Oncology, Urology, Pathology, Radiology Departments with the Laboratory of Medical Genetics and RNA Biology of Humanitas University

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Study participants will be genetically screened for the DRG mutation they are likely to have and positive individuals will be monitored by digital rectal examination (DRE) and checking Prostate Health Index (PHI). Patients with positive DRE will receive a prostate biopsy, the others will be tested for PHI. In case of PHI>40, patients will receive an mpMRI, according to EAU guideline, and a systematic prostate biopsy plus a software fusion-guided target biopsy if mpMRI showed at least a PIRADS>2 lesion. In case of PHI 20-40, patients will undergo mpMRI and fusion-guided target biopsy when PIRADS>2 plus systematic random biopsy. Patients with a negative mpMRI (PIRADS<3) will be screened by PHI/DRE annually. In case of PHI<20, patients will be screened by DRE/PHI annually. In case of biopsy positive for PCa, patients will be consulted for precision therapy. Correlation of pathological data and clinical outcome with molecular characteristics in patients identified by our enhanced screening and in those selected by NGS analysis (i.e. positive for a DRG mutation). The latter will be follow-up as benchmark for understanding the clinical course of PCa with DRG defects

1. Select a cohort of "healthy" men with a DRG mutation and enroll them in a target screening program for early PCa detection.
2. Demonstrate that the identification of high-risk individuals can: i) detect undiagnosed PCas, ii) improve early diagnosis, iii) impact on clinical management (PARP inhibitors, immunotherapy).
3. Better understand the molecular and clinical characteristics of PCa associated with DRG defects

- Determine the clinically significant percentage of PCa in total prostatic neoplasms;
- Compliance to attend the "enhanced" screening (Descriptive analysis);
- Stratification according to age at diagnosis of PCa (Descriptive analysis);
- Correlation with pathological outcome in patients who will undergo to radical prostatectomy (Descriptive analysis + comparative analysis: ANOVA):
- Incidence of biochemical recurrence (BCR) (Descriptive analysis)
- Correlation of pathological data and clinical outcome (BCR) with molecular characteristics in both patients identified by our enhanced screening and those identified by the NGS analysis (i.e. positive for a DRG mutation) (Descriptive analysis + KM curves recurrence fre-survival or progression to Metastasis free survival)
- Comparison of the mutational burden in DRG mutation positive vs. DRG mutation negative PCa (Descriptive analysis).

Main technical approaches

The PhD will be a postgraduate medical doctor who gained the fellowship (specialisation) in Urology. His/her task will be focused on patients' selection by counselling them for high-risk developing PCa. He/she will be involved in all the steps of clinical evaluation of patients and cases. He/she will take care of screening and physical examination and perform the software assisted target biopsies and systematic biopsies. He/she will bridge the clinical data with genetic data and will be involved in the clinical follow-up of patients.

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Scientific references

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Type of contract

Scholarship of € 21.000 gross per year awarded by Istituto Clinico Humanitas. This sum is subject to IRPEF income tax and exempt from social security contributions.
For physicians registered to the professional register, contract for continuative and coordinated service of at least € 26.000 activated Istituto Clinico Humanitas. This sum is subject to IRPEF income tax.

Borsa di studio pari ad almeno € 26.000 annui lordi erogata da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF ed esente da contribuzione previdenziale.

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Per medici iscritti all'albo, contratto collaborazione coordinata e continuativa (cococo) pari ad almeno € 26.000 annui lordi attivato da Istituto Clinico Humanitas. Importo soggetto a tassazione IRPEF.

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