Prostate cancer (PrCa) is the most common cancer and the 2nd leading cause of cancer mortality among men in Western countries. Despite advances in diagnosis and early-disease treatment, up to 30% of PrCa patients will develop metastasis at some point and succumb after the acquisition of a castration-resistant status (mCRPCa). The early identification of PCa patients with greater predisposition to develop aggressive mCRPC could lead to the development of novel treatment strategies and improved outcomes. In addition to AR aberrations following androgen-deprivation therapy leading to resistance to current treatment options, DNA repair defects have been identified in about 5% and 25% of early PrCa and mCRPC patients, respectively. Seminal work from our Group, and others, has established that some alterations, e.g. germline BRCA1/BRCA2, ATM, ATR, and ATM, ATR, and impact of DNA repair germline mutations in mCRPC survival and treatment outcome in advanced patients with advanced solid malignancies. Heterogeneity and clonal diversity was established based on the frequency and distribution of different dominant events of fusion gene status versus histology on risk-stratification for rhabdomyosarcoma of fusion gene status versus histology on risk-stratification for rhabdomyosarcoma.

RESEARCH HIGHLIGHTS

PROCURE biomarkers platform

This network was started by our Group in 2013; it currently has 5 ongoing prospective studies (PROREPAIR, PROSTAC, PROSABI, PROSENZA, PRORADIDUM) in mCRPC in 63 participating centres with over 900 enrolled patients.

PROREPAIR study

This is a prospective multicentre cohort study involving 50 Spanish centres within the PROCURE network. By April 2016, 432 mCRPC patients were enrolled to evaluate the prevalence and impact of DNA repair germline mutations in mCRPC survival and the response to systemic treatments for mCRPC. Germline mutations were analysed in the following genes: ATM, ATR, RAD51, BRCA2, BRCA1, BRIPI, CHK2, GEN1, MSH2, MSH6, MLH1, MRE11A, MSH2, MSH6, NBN, PALB2, PMS2, RAD51C, RAD51D and XRCC2. Current results suggest that up to 12% of the patients in this series harbour a germline deleterious mutation. Analyses of the clinical impact of germline and somatic mutations in outcomes are still undergoing. BRCARAD and BRCAPIR2OS studies, although in a retrospective fashion, will address similar questions at an early prostate cancer stage.

SWITCH Phase II study

In 2016, we also completed the enrolment and follow-up of our first clinical trial, ‘Phase II pilot study of the prednisone to dexamethasone switch in mCRPC patients with progression on abiraterone and prednisone’, aimed at analysing the role of certain steroids in the resistance and response to novel androgen-synthesis inhibitors in 26 patients. A simple change in prednisone to dexamethasone rescued the sensitivity to abiraterone and prolonged the time benefiting from this treatment in 40% of the patients; such responses could be linked to AR mutations detected in ctDNA.

Biological characterisation of BRCA2 and ATM mutated tumours

Initial results from human tumour characterisation and mouse models conducted by our Group support that BRCA2 germline and/or somatic alterations may occur early in cancer progression, and that ATM aberrations will favour cancer progression and early intratumour heterogeneity.