OVERVIEW

Prostate cancer (PrCa) is the most common cancer and the second leading cause of cancer mortality among men in Western countries. Despite the advances in PrCa diagnosis and early-disease treatment achieved over the last 25 years, up to 20% of PrCa patients will still develop metastatic disease at some point. The majority of these metastatic PrCa patients will succumb after the acquisition of a castration-resistant status (Castration Resistant Prostate Cancer: CRPC), even when treated with novel therapies that have shown to improve survival and quality of life (QoL) in this advanced-resistant setting. The early identification of PrCa patients who have a more aggressive biology and a greater predisposition to develop aggressive metastatic disease could lead to improved outcomes. Currently, we lack the adequate biological knowledge and reliable biomarkers to select the right treatment for the right patient at the right time.

RESEARCH HIGHLIGHTS

DNA repair defects in early prostate cancer

The driving androgen receptor (AR) signalling in PrCa has been implicated in the acquisition of DNA damage, such as single-strand breaks (SSBs) and double-strand breaks (DSBs). Interestingly, AR activity also regulates a network of DNA repair genes. Genes directly regulated by the AR are involved in homologous recombination (HR) DNA repair pathways. To date, a small number of familial cancer syndromes have been associated with an increased risk of prostate cancer. The majority of these genes are associated with inherited mutations in HR DNA repair genes (e.g. BRCA2, BRCA1, PALB2, and XRCC3) or DNA damage sensors/check points (e.g. CHK2) that directly activate HR. We have investigated the effect of inherited BRCA mutations on conventional treatments for localised and locally advanced PrCa as a model of sporadic aggressive PrCa. We have previously shown that BRCA carriers have worse outcomes than non-carriers, when conventionally treated with radiotherapy or prostatectomy, as they relapsed and progressed earlier to lethal metastatic disease. In 2015, we have shown that, despite of their aggressive behaviour, BRCA mutated tumours are androgen-dependant, which is of relevance for tailored treatment. We are currently working on the molecular characterisation of BRCA mutated PrCs, in collaboration with the Institute of Cancer Research (UK), KconFab and the Peter McCallum Cancer Centre (Australia), as well as several Spanish centres. In 2015, we have also identified several features, previously associated with poor PrCa outcome, to be significantly more common in BRCA2 mutated PrCs than in sporadic tumours, which may help to explain their adverse prognosis and be of relevance for targeted therapies.

Circulating biomarkers in CRPC

In the current metastatic CRPC scenario, there are several drugs with diverse mechanisms showing activity in a subset of patients, while others remain primarily resistant. The efficient ‘a priori’ discrimination between both populations is still required. The development of novel biomarkers, which are truly indicative of the tumour biology and/or the tumour-host interaction, should facilitate individual patient risk stratification and improve treatment benefit prediction. We have launched a network of 55 centres across Spain (the PROCURE platform) in order to conduct several prospective, multicentre, and parallel biomarker studies in patients receiving docetaxel, cabazitaxel, radium-223 or abiraterone acetate; these studies will involve over 800 CRPC patients during the next 5 years. With these studies, we aim to analytically qualify and clinically validate a series of blood-borne biomarkers including ctDNA, ctRNA, exosomes and CTCs. Its characteristics make this study unique in the CRPC field.