PROSTATE CANCER JUNIOR CLINICAL RESEARCH UNIT

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OVERVIEW

Prostate cancer remains a major health burden as over a million men around the world are annually diagnosed with prostate cancer. Up to 30% of them may develop metastatic prostate cancer, which is the advanced form of this disease, once it has spread outside the prostate and is no longer curable. This metastatic stage causes about 6,000 deaths every year in Spain alone, whilst in the US over 30,000 men succumb to the disease every year. In recent years, different subtypes of prostate cancer have been identified based on different genomic profiles. We believe that a better understanding of cancer biology, as well as an improved human prostate cancer taxonomy linked to clinical outcomes, could lead to improved patient outcomes through the application of tailored treatment strategies as opposed to the current one-fits-all approach. As an example of one of these clusters, 20-25% of all metastatic prostate cancers have aberrations in DNA repair genes; about half of these clusters, 20-25% of all metastatic prostate cancers, may correspond to inherited mutations. The highlights of this study can be briefly summarised as follows: up to 16% of mCRPC may carry germline pathogenic mutations in DDR genes; a BRCA2 germline mutation has twice the risk of progressing to castration-resistant disease and of death from prostate cancer. We have just started analysing the prevalence of somatic aberrations in DDR genes in this study as part of a DoD IMPACT award. In addition, we are completing the genomic and transcriptomic characterisation of a large collection of BRCA2 mutated prostate cancers in order to identify secondary events that may contribute to the poor prognosis of the affected men.

RESEARCH HIGHLIGHTS

During 2018, our Group made significant progress in many projects. We finalised the primary analyses of our PROREPAIR-B study and have also completed recruitment in 3 additional studies from our PROCURE platform of prospective biomarker studies: PROSTAC, PROSKARI & PRORADIANUM. Over 1,000 men with metastatic castration-resistant prostate cancer (mCRPC) have been enrolled in these studies to this day. Our clinical CNIO-IBIMA unit has been consolidated as one of the top prostate cancer clinical trials units in Europe, playing a leading role in several early and pivotal clinical trials. We have also reported our first investigator-initiated phase II study. At the preclinical level, we have made some advances in the characterisation of the biological role in prostate cancer of different DDR defects, including Atm loss. We have also made progress in developing representative in vivo models of metastatic prostate cancer and patient-derived-xenografts.

PROREPAIR-B study. The primary analyses of the PROREPAIR-B study will be published early in 2019 in the Journal of Clinical Oncology. The highlights of this study can be briefly summarised as follows: up to 16% of mCRPC may carry germline pathogenic mutations in DDR genes; a BRCA2 germline mutation has twice the risk of progressing to castration-resistant disease and of death from prostate cancer. We have just started analysing the prevalence of somatic aberrations in DDR genes in this study as part of a DoD IMPACT award. In addition, we are completing the genomic and transcriptomic characterisation of a large collection of BRCA2 mutated prostate cancers in order to identify secondary events that may contribute to the poor prognosis of the affected men.

AR gain and mCRPC treatment selection. As part of an ongoing international collaboration with Dr Attard’s lab (UCL, London) and Dr di Giorgi’s team (BCSS, Meldola), we have determined that mCRPC, having a normal number of copies of the androgen receptor (AR) gene in ctDNA, have a lower risk of disease progression and a higher life expectancy when they are treated with abiraterone/ezalutamide, with a 50% improvement compared to docetaxel. On the other hand, the patients with more copies of the AR gene respond slightly better to docetaxel.

SWITCH phase II study. This study, recently published in the British Journal of Cancer, demonstrated that the simple change of the supporting steroid, switched from prednisone to dexamethasone, while maintaining abiraterone, helps to re-induce the response to abiraterone in about 4 out of every 10 patients progressing by PSA criteria. This response does not occur in patients with AR gain detected in plasma ctDNA, while patients with AR normal status benefit the most.

PUBLICATIONS

- Romero-Laudert N et al. (2018). Phase II pilot study of the predictions to dexamethasone switch in metastatic castration-resistant prostate cancer (mCRPC) patients with limited progression on abiraterone plus prednisone (SWITCH study), Br J Cancer. 119(3), 266-276.

AWARDS AND RECOGNITION

- Member of the Board of Directors, European Organization for Research and Treatment of Cancer (EORTC).
- Elena Crespo: Faculty Board Member, ESMO Preceptorships in Prostate Cancer.
- Rebeca Lozano was awarded the ‘Merit Award’, American Society of Clinical Oncology EU Cancers Symposium, San Francisco. ‘Best Communication’ Award, 2018 ESMO annual Meeting, and the Ro Hortega Fellowship 2019, Instituto de Salud Carlos III, Spain.

Figure PROREPAIR-B study. Distribution of the pathogenic mutations in DDR genes identified in the study (top). Kaplan-Meier curves for cause-specific survival from diagnosis of mCRPC, BRCA2 mutant in noncarriers (bottom).