DNA repair as a treatment target

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A critical link exists between genomic instability and cancer development. This instability can manifest as small changes at the nucleotide level or as gross chromosomal alterations. Mutations in the genes that encode DNA damage response proteins are responsible for a variety of genomic instability syndromes including Hereditary Non-Polyposis Colorectal Carcinoma, Bloom syndrome, Ataxia-telangiectasia, BRCA1 and BRCA2 mutated breast and ovarian cancers and Fanconi anaemia. Similarly epigenetic silencing of genes associated with the maintenance of genomic stability have also been implicated in the pathogenesis of cancer. Here, I discuss how different tumours may be classified not only by tumour site but also by the type of underlying genetic instability. This type of classification may assist in the optimization of treatment regimens as well as informing the development of new therapeutic approaches.

Disclosure: Professor Ashworth may benefit financially from the development of PARP inhibitors through patents held jointly with KuDOS–AstraZeneca through the Institute of Cancer Research “rewards to inventors” scheme.

EARLY PHASE PROOF OF CONCEPT STUDIES AND RATIONALE FOR PATIENT SELECTION

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Epithelial carcinomas are thought to occur following the acquisition of, and selection for, multiple mutations in a parental somatic cell clone. In the last two decades the role of genome caretakers, which function in key areas of the DNA damage response, have been recognised as important tumour suppressor genes. Loss of function of these genes occurs as a result of mutations in the germline and (or) as somatic mutations or epigenetic events. In each case, loss of function in a tumour cell pre-cursor clone leads to accelerated mutation acquisition that underpins the etiology of the tumour. The basic biology of DNA repair and evidence for loss of function in cancer will be elaborated in Professor Ashworth’s preceding lecture. In this lecture I will describe trials testing chemotherapeutic drugs that seek to target these abnormalities in the DNA damage response for therapeutic gain. Many established cancer chemotherapeutics exert their effect by creating DNA damage that has some selectivity for tumour cells. Matching the appropriate DNA damaging agent to susceptible repair deficient tumour types may improve outcomes. Novel therapies, such as PARP inhibitors, that themselves inhibit DNA repair, have recently been described. The results of the first trials that explore a “synthetic lethal” approach that combines drug induced and inherent tumour DNA repair defects are emerging and will be reviewed. Putative approaches for breast cancer patient selection will be discussed. In contrast to the role of some tumour suppressor genes and oncogenes, continued loss of function of genome caretakers may not confer a continuing selective tumour survival advantage after the establishment of the fully malignant phenotype. A selective pressure may exist for tumour cells to regain DNA repair functions during DNA damaging therapy. The evidence for these potential resistance mechanisms will also be reviewed.

Disclosure: Dr Andrew Tutt declares that he has received honoraria for speaking at educational meetings and has sat on advisory boards for Astra Zeneca, Pfizer and Sanofi Aventis.

EARLY DATA AND FUTURE PLANS FOR COMBINATIONS OF PARP INHIBITORS AND CHEMOTHERAPY

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Poly (ADP-ribose) polymerase (PARP) inhibitors have emerged as a class of new promising agents that are being evaluated in the oncology field both as single drugs and in combination with chemotherapy. PARP inhibitors target PARP-1, an enzyme that plays a key role in the base excision repair (BER) pathway, one of the main mechanisms to repair DNA single strand breaks (SSB) and gaps. Inhibition of DNA damage repair with these agents has been proposed as a strategy to increase the effectiveness of DNA-damaging therapies. In different preclinical models of tumor progression and in vitro cytotoxic studies it was demonstrated that PARP inhibitors enhanced the efficacy of alkylating agents (particularly temozolomide), topoisomerase I poisons (irinotecan, topotecan), cross-linking drugs (platinum, mitomycin C), and radiation. This observation led to different clinical trials of PARP inhibitors in combination with chemotherapy in patients with advanced solid tumors. The first clinical results in triple negative breast cancer patients with metastatic disease were communicated at ASCO’09 and SABCS’09 by J. O’Shaughnessy and colleagues. They reported the results of a phase II trial with carboplatin plus gemcitabine alone or in combination with BSI-201 (a PARP inhibitor). A statistically significant difference was found in progression free survival (7.2 months vs 4.1 months (HR 0.49, 0.30-0.79 95%CI, p <0.003)) and in median overall survival (10.6 months versus 7.6 months, (HR 0.48, 0.28-0.82 95%CI, p =0.006)). Combinations of PARP inhibitors with cisplatin, carboplatin, carboplatin + gemcitabine, taxanes, irinotecan, temozolomide, bevancizumab and others are currently under investigation in several phase I-II trials. In addition, recent preclinical evidence encourages the assessment of PARP inhibitors in monotherapy in tumors with homologous recombination defects other than BRCA-mutants (ie, PTEN, RAD51, ATM, CHK...). Finally, the search of the most synergistic drug combinations with PARP inhibitors have recently been assessed in vitro and in vivo mice with BRCA2-deficient mammary tumors. Current challenges with these compounds include identification of biomarkers of response, recognize adequate regimens of combination without an increasing toxicity, and overcome potential mechanisms of resistance.

Disclosure: J. Balmaña is a co-investigator in an ongoing phase I trial with Olaparib (AZ).