investigating how the OVH model should be modified to be suitable as a plan QA tool for prostate patients.

Symposium: Targeting DNA repair / DDR pre-clinical evidence

SP-0194
Tumour-specific radiosensitisation by ATR inhibitors
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The human ataxia telangiectasia and Rad3-related protein (ATR) kinase is activated by DNA damage and replication stress as a central transducer of a checkpoint signaling pathway. Subsequent to activation, ATR phosphorylates many substrates, including the kinase Chk1, which regulates cell-cycle progression, replication fork stability, and DNA repair. All of the three mentioned events promote cell survival during replication stress and in cells with DNA damage. It was hypothesized that ATR inhibitors would be therapeutically useful, with a predicted specificity for tumors sparing normal cells. Since the introduction of potent ATR inhibitors a hand full of studies in conjuction with radiotherapy has been published including our own work where we showed sensitization of pancreatic cancer in vitro and in vivo to radiotherapy in conjuction with VE-822 (∼XV-970), an ATR inhibitor. The drug decreased maintenance of cell-cycle checkpoints, increased persistent DNA damage and increased homologous recombination in irradiated cancer cells. Furthermore, we observed decreased survival of pancreatic cancer cells but not normal cells in response to XRT or gemcitabine. VE-822 markedly prolonged growth delay of cancer cells but not normal cells in response to XRT or gemcitabine. The first clinical early phase trials combining ATR inhibitors with radiotherapy or chemotherapy are underway to generate first clinical early phase trials combining ATR inhibitors with radiotherapy or chemotherapy are underway to generate important insights into the effects of ATR inhibition in humans and the potential role of inhibiting this kinase in the treatment of human malignancies.

SP-0195
Inhibition of ATR kinase activity for the treatment of lung cancer
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ATR and ATM are protein kinases activated at stalled and collapsed replication forks and DNA double-strand breaks (DSBs), respectively, where they function to maintain genome integrity by mediating cell cycle checkpoints and DNA repair. ATM has been widely studied since ataxia telangiectasia individuals who express no ATM protein are the most radiosensitive humans identified. It has therefore been postulated that ATM kinase inhibitors (ATMi’s) will increase the efficacy of radiotherapy. ATR has also been widely studied, but advances have been complicated by the finding that ATR is an essential protein in mice and mammalian cells. Nevertheless, pharmacologic ATR and ATM kinase inhibitors have been identified and these sensitize cancer cells to ionizing radiation (IR) in tissue culture. ATR kinase inhibitors (ATRi’s) also synergize with cisplatin to induce cell death in tissue culture. Since concurrent cisplatin and radiation is used as standard of care for locally advanced and metastatic NSCLC patients, ATR kinase inhibition may significantly improve the efficacy of first line treatment in tens of thousands of patients in the USA every year. Until recently, however, in vivo studies have been limited by the absence of bioavailable ATR and ATM kinase inhibitors. Here we describe orally active and bioavailable ATR and ATM kinase inhibitors and show that, in contrast to expectations, ATRi is surprisingly well tolerated. We show that cisplatin-ATRi induces a complete response in ATM-deficient lung cancer xenografts and potentiates the effect of cisplatin in p16INK4a-deficient lung cancer xenografts. We also show that conformal radiation-ATRi and radiation-ATMi induce profound responses in an autochthonous KrasG12D/Twist1 mouse model of lung adenocarcinoma, and that the efficacy of radiation-ATRi for the treatment of lung cancer appears to be better than that of radiation-ATMi due to lower toxicity.

SP-0196
Realising the full potential of DNA damage response inhibition in the treatment of cancer
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An underlying hallmark of cancers is their genomic instability, which is associated with a greater propensity to accumulate DNA damage. Historical treatment of cancer by radiotherapy and DNA-damaging chemotherapy is based on this principle, yet it is accompanied the significant risk of collateral damage to normal tissue and unwanted side effects. Targeted therapy based on inhibiting the DNA damage response (DDR) in cancers, either alone or in combination, offers the potential for a greater therapeutic window by tailoring treatment to patients with tumours lacking specific DDR functions. The recent approval of olaparib (Lynparza), the poly(ADP-ribose) polymerase (PARP) inhibitor for treating tumours harbouring BRCA1 or BRCA2 mutations, represents the first medicine based on this principle, exploiting an underlying cause of tumour formation that also represents an Achilles’ heel. Different forms of DNA damage evoke responses by different repair mechanisms and signalling pathways and the choice of pathway will also be influenced by the phase of the cell cycle in which the damage occurs. DDR represents a good source of anticancer drug targets as there are at least three key aspects of DDR that are different in cancers compared with normal cells. These are a) the loss of one or more DDR capability b) the increased levels of replication stress and c) the higher levels of endogenous DNA damage in cancer cells compared to normal cells. This talk will focus on examples of how each of these concepts is currently being exploited to treat cancer. As an example of the exploitation of the first concept, the use of PARP inhibitors to treat cancers deficient in BRCA1 and BRCA2 gene function, as well as other homologous recombination repair deficiencies, will be presented. The second concept - the exploitation of high levels of replication stress in cancers, will be exemplified through data presented resulting from the use of inhibitors of ATR and WEE1. As part of the discussion on how best to exploit the higher levels of endogenous DNA damage in cancers, the focus will be on the challenges associated with expanding the therapeutic window for the use of DDR inhibitors in combination with DNA damaging agents such as radiation and chemotherapy. Finally, the ambition of how best to realise the full potential of DNA damage response-based therapy will be discussed including the use of different synergistic combinations in a personalized healthcare approach.

Figure highlighting the differences in cancer DNA damage response compared to normal cells that provides the