Pancreat Disord Ther 2016, 6:4(Suppl)
http://dx.doi.org/10.4172/2165-7092.C1.003

Exploiting an NQO1-mediated 'kiss of death' for pancreatic cancer therapy

David A Boothman
University of Texas, USA

Unique NAD(P)H:quinone oxidoreductase 1 (NQO1) bioactivatable drugs (e.g., ß-lapachone-ARQ761 in clinical form) take advantage of elevated NQO1:catalase ratios in most solid cancers, and in pancreatic cancers in particular. ß-Lapachone elicits tumor-selective DNA damage that can be exploited in a variety of ways to selectively target pancreatic cancer. ß-Lapachone-exposed NQO1+ cancer cells are killed independent of oncogenic driver or passenger mutations, independent of p53 status, cell cycle status, and/or bak/bax loss. A major discovery recently made is that NQO1 bioactivatable drugs can be used to make DNA repair inhibitors (e.g., inhibitors of DNA base excision repair (BER) or PARP inhibitors) tumor-selective. When combined with inhibitors of BER, NQO1+ cancers are specifically targeted by NAD+-Keresis, a form of programmed necrosis. In contrast, when PARP inhibitors and ß-lapachone are combined, enhanced antitumor activity results from sustained NAD(P)H levels that refuel NQO1-dependent futile redox drug recycling. Significant oxygen consumption rate/reactive oxygen species burst causes dramatic increases in DNA lesions (particularly DNA base, single and double strand breaks) that are not repaired due to PARP inhibition. Cancer metabolism, cell signaling and overall cell death switches from ß-lap-induced PARP1 hyper-activation-mediated NAD+-Keresis to tumor-selective, caspase-dependent apoptosis specifically in NQO1+ cancers. Such therapy is particularly applicable to recalcitrant pancreatic and non-small cell lung cancers, but can be applied to most solid cancers. Preclinical, pharmacokinetic (PK), pharmacodynamic (PD) results using novel nano-particle delivery systems, as well as Phase-I b clinical trial results with ARQ761 mono-therapy, will be discussed. Molecular PARylation landscaping (defining the Asp- and Glu-ADP-ribosylated proteome) in collaboration with Dr. Yonghao Yu, to delineate novel DNA repair-related pathways using ß-lapachone will also be discussed.

David.Boothman@UTSouthwestern.edu

Pancreas transplant postoperative protocols: How it relates to preventative measures for readmittance after discharge

Devin Barrett
Home Health and Infusion Options, USA

In summary, Home Health and Infusion Options (HHIO) has been coordinating care for transplant patients postoperatively for five years. This care includes, but is not limited to, coordinating hi-tech skilled nursing and hydration coverage. As an advocate for the patient, HHIO works with highly skilled nurses and pharmacies that monitor the patient with clinical documentation and ongoing communication with the patient's transplant team. A majority of Chicago's transplant centers do not follow the same care pathway from hospital to home, allowing a gap in proper patient discharge. Pancreas transplant patients have a higher risk of dehydration leading to re-admission due to a lack of established care pathways and protocols. Through HHIO based qualitative research, the results can be interpreted on why hydration care pathways should be established in every transplant center, therefore reducing readmission rates due to dehydration. In conclusion, by implementing a protocol that includes solutions to alleviate dehydration and readmittance, patients are able to focus on their health and rebuilding their life post-transplant.

devin@hhio.net