Session 6: Antitumoral Activity of Nitric Oxide-Based Releasing Strategies: Clinical Trials Moderator: Dr. Benjamin Bonavida INVITED SPEAKERS

The Development Of RRx-001, A Novel Nitric-Oxide-Mediated Epigenetically Active Anticancer Agent

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Background: RRx-001 is a novel NO and hypoxia mediated anticancer agent with epigenetic activity. In the first-in-human, Phase I trial, 5/5 patients who progressed on RRx-001 treatment were resensitized to previously refractory therapy, hinting at a generalized resensitization effect.
Aims: A randomized open-label multi-part, multi-center phase II trial of RRx-001 versus regorafenib (ROCKET) has commenced to explore the resensitization and/or 'episensitization' potential in irinotecan refractory tumors and its impact on overall survival.
Methods: Patients with irinotecan-refractory metastatic colorectal cancer with an ECOG PS 0–1 who progressed on oxaliplatin-, and irinotecan-based regimens with or without bevacizumab, cetuximab or panitumumab are randomized 2:1 to receive RRx-001 16.5 mg/m^2 IV 1x/week or regorafenib 160 mg orally 21 of 28 days until progression or unacceptable toxicity followed by treatment with refractory irinotecan-based therapies.
Results: To date, 26 patients have been randomized with 18 patients evaluable for resensitization. Post RRx-001 patients demonstrated marked decreases in CEA in 12/13 patients as compared to 5 patients receiving regorafenib who were too systemically unwell to proceed to subsequent treatment. Progression free survival (ongoing) for RRx-001+irinotecan is 4.9 months compared 1.8 months on Regorafenib+irinotecan.
Conclusion: Early results in the ROCKET study suggest that RRx-001-mediated resensitization to previously refractory therapies may have a generalized effect, independent of KRAS or p53 status. These early results are intriguing, suggesting improved QOL and overall survival over currently approved therapy in the chemotherapy refractory colorectal cancer.

http://dx.doi.org/10.1016/j.redox.2015.09.035

Treatment Of Sunitinib-Induced Hypertension In Solid Tumors By Nitric Oxid Donors

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Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are overexpressed in the majority of renal cell carcinomas (RCC). This characteristic has supported the rationale of targeting VEGF-driven tumour vascularization, especially in clear cell RCC. VEGF-inhibiting strategies include the use of tyrosine kinase inhibitors (sunitinib, axitinib, pazopanib, and sorafenib) and neutralizing antibodies such as bevacizumab.

Hypertension (HT) is one of the most common adverse effects of angiogenesis inhibitors. Hypertension observed in clinical trials appears to correlate with the potency of VEGF kinase inhibitor against VEGFR-2: agents with higher potency are associated with a higher incidence of hypertension. Although the exact mechanism by TKIs induce hypertension has not yet been completely clarified, two key hypotheses have been postulated. First, some studies have pointed to a VEGF inhibitors-induced decrease in nitric oxide synthase (NOS) and nitric oxide (NO) production, that can result in vasoconstriction and increased blood pressure. VEGF, mediated by PI3K/Akt and MAPK pathway, upregulates the endothelial nitric oxide synthase enzyme leading to up-regulation of NO production. So inhibition of signaling through the VEGF pathway would lead to a decrease in NO production, resulting in an increase in vascular resistance and blood pressure. Secondly a decrease in the number of microvascular endothelial cells and subsequent depletion of normal microvessel density (rarefaction) occurs upon VEGF signaling inhibition.

http://dx.doi.org/10.1016/j.redox.2015.09.036

The Role Of Nitric Oxide After Repeated Low Dose Photodynamic Treatments In Prostate Carcinoma Cells

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Photodynamic therapy (PDT) is a clinically approved treatment that causes a selective cytotoxic effect in cancer cells. In addition to the production of singlet oxygen and reactive oxygen species, PDT can induce the release of nitric oxide (NO) by up-regulating nitric oxide synthases (NOS). Since non-optimal PDT often causes tumor recurrence, understanding of the molecular pathways involved in the photoprocess is a challenging task for scientists. The present study has examined the response of the PC3 human metastatic prostate cancer cell line, following repeated low-dose pheophorbide *a* treatments, mimicking non-optimal PDT treatment. The analysis was focused on the NF-kB/YY1/RKIP circuitry as it is (i) dysregulated in cancer cells (ii) modulated by NO and (iii) correlated with the epithelial to mesenchymal transition (EMT). We hypothesized that a repeated treatment of non-optimal PDT

induces low levels of NO that lead to cell growth and EMT via regulation of the above circuitry. The expressions of gene products involved in the circuitry and in EMT were analyzed by western blot. The findings demonstrate the cytoprotective role of NO following non-optimal PDT treatments that was corroborated by the use of L-NAME, an inhibitor of NOS.

http://dx.doi.org/10.1016/j.redox.2015.09.037