allied academies

International Conference on
GASTROENTEROLOGY

June 25-26, 2018 | Dublin, Ireland

J Gastroenterol Dig Dis 2018, Volume 3

EFFECTS OF PROSPECTIVE METFORMIN ADMINISTRATION ON ANTICANCER THERAPY AND CANCER STEM CELLS IN PATIENTS WITH GI AND OTHER MALIGNANCIES

Wasif M Saif and **Robert E Martell**
Tufts University School of Medicine, USA

Background: Observational studies have demonstrated association of Metformin with reduced cancer incidence and mortality in multiple cancer types. The anti-neoplastic effects of metformin are believed through many mechanisms including activation of AMP-activated protein kinase, which controls the mammalian target of rapamycin (mTOR) growth regulatory pathway.

Patients & Methods: We conducted delayed start randomized trial of non-diabetic patients in two stages: patients were randomized to two arms during stage I - concurrent arm (metformin + chemo) vs. delayed arm (chemo alone) and in stage two, patients in delayed arm were crossed over to receive metformin. Patients received metformin 500 mg twice daily + chemotherapy to define DLTs in both stages. Translational correlates included effects of metformin on expression and phosphorylation of AMPK by western blot in PBMCs. In another pilot study, we evaluated the safety and impact of pretreatment with metformin on colorectal cancer stem cells (CCSC) in patients undergoing resection and evaluate the effects of metformin on the expression of CCSC markers by measuring relative mRNA levels of CD133, OCT4 and NANOG using RT-PCR and immunohistochemistry.

Results: In the randomized study, DLTs seen only included those associated with established chemo AEs. No lactic acidosis or hypoglycemia occurred. Restaging showed stable disease in 46% and 28% of patients had decline in tumor markers. Analysis of phospho-AMPKα showed that phosphorylation of AMPKα was increased after metformin (mean=1.114±0.512) and analysis of total levels of AMPKα showed similar results (mean=1.04±0.28). In the pilot study on patients undergoing surgery, no grade three or four AEs related to metformin including hypoglycemia and lactic acidosis were observed. No unexpected post-operative complications were witnessed. CCSC markers showed decrease in expression of CD133, OCT4 and NANOG following metformin.

Conclusions: Our studies include the largest prospective study in cancer patients who received metformin in combination of chemotherapy and the first one that prospectively demonstrates the impact of metformin on AMPK phosphorylation and impact on CCSC. These preliminary data warrant further investigation to explore the benefits of metformin both as a chemotherapeutic and chemopreventive agent in adequately powered prospective studies.

WSaif@tuftsmedicalcenter.org