Clinical Cancer Research Highlights

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Selected Articles from This Issue

Gender, Cytidine Deaminase, and 5-Aza/Decitabine

Mahfouz *et al.* _____Page 938

The cytidine analogues 5-azacytidine and decitabine have a powerful molecular epigenetic effect: depletion of DNA-methyltransferase. This is an S-phase, DNA-replication dependent action, so treatment exposure time is likely a crucial determinant of efficacy, and genetic factors that influence cytidine analogue metabolism could potentially affect treatment outcomes. The ubiquitously expressed enzyme cytidine deaminase (CDA) rapidly inactivates 5-azacytidine/decitabine. Mahfouz and colleagues evaluated here for the first time the impact of pharmacogenetic factors that affect CDA enzyme activity/expression on 5-azacytidine/decitabine treatment outcomes. Interestingly and significantly, they found that gender had a substantially greater influence on CDA enzyme activity/expression than the well-known CDA SNP A79C, with a corresponding impact on overall survival in 5-azacytidine/decitabine-treated MDS patients. The identification of this pharmacogenetic factor and the mechanism by which it affects outcomes suggest rational methods for optimizing the clinical application of these unique oncotherapeutics.

Lactate Dehydrogenase B Is Required for KRAS-Driven Lung Cancer

McCleland *et al.* _____Page 773

KRAS hyperactivation can occur through mutation or genomic amplification and defines a subset of lung tumors with poor prognosis and fewer therapeutic options. McCleland and colleagues utilize both functional and genomic techniques to identify genes that functionally cooperate with KRAS. These integrative approaches identify lactate dehydrogenase B (LDHB) as overexpressed and necessary for cell growth in the context of KRAS-hyperactive lung cancers. Consistent with a role for LDHB in glycolysis and tumor growth, lung cancers with high LDHB show an increased dependence on glycolysis and a worse patient outcome. These findings warrant further investigation of LDHB as a metabolic driver in KRAS-dependent lung cancer.

Human OATP1A/1Bs in Paclitaxel and Methotrexate Disposition

van de Steeg *et al.* _____Page 821

Cancer chemotherapy is complicated by interindividual variation in drug response and toxicity and drug–drug interactions. Given their tissue distribution and broad substrate specificity, drug uptake transporters of the organic anion transporting polypeptide (OATP) family may play a marked role in these processes. Using humanized OATP1B1, OATP1B3, and OATP1A2 transgenic mice, van de Steeg and colleagues found that all 3 OATPs transport the anticancer drug methotrexate *in vivo*, whereas OATP1B3 and OATP1A2 transport paclitaxel. Variation in OATP1A/1B activity due to genetic variation or drug–drug interactions, and tumor-specific expression of OATPs, might therefore codetermine treatment efficacy and/or toxicity of these, and likely many other, anticancer drugs.

Circulating VEGF-A as a Biomarker for Bevacizumab

Hegde *et al.* _____Page 929

There has been significant interest in fully understanding the ability of plasma VEGF-A to predict for patients who may respond favorably to bevacizumab, an antiangiogenesis agent approved for metastatic cancers including colorectal cancer (CRC), non–small cell lung cancer (NSCLC), and renal cell cancer (RCC). Previous studies have examined small cohorts or single clinical trials that are underpowered for retrospective subset analyses. To provide a more definitive answer, Hegde and colleagues evaluated VEGF-A levels in plasma from 1,816 patients from 5 randomized controlled trials in indications including CRC, NSCLC, and RCC. Using an assay that recognizes major isoforms of VEGF-A with equivalent sensitivities, this study provides robust data on prevalence of plasma VEGF-A in these indications. This study shows for the first time in a rigorous manner that plasma levels of total VEGF do not predict benefit from bevacizumab therapy in these indications.

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