Impact of Direct Acting Antivirals on Survival in Patients with Chronic Hepatitis C and Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) represents a global public health burden, affecting an estimated 14 million persons worldwide, and is the third leading cause of cancer mortality. Within the United States, HCC is ranked 7th for cancer related mortality and has seen a doubling in incidence from 1975 to 2007. The primary predisposing factors for HCC carcinogenesis is liver cirrhosis. Cirrhosis risk factors include chronic alcohol use, viral hepatitis, including hepatitis c (HCV), and non-alcoholic fatty liver disease. Chronic HCV infection is the second most common risk factor for HCC and is responsible for 1025% of all HCC cases. Over 2030 years, 2030% of patients with chronic HCV infections will develop cirrhosis and end stage liver disease and 14% of these patients will progress to HCC each year. Of all HCV related HCC cases, 8090% occur in the setting of cirrhosis. With more than 3.5 million HCC patients in the United States and an estimated 130170 million patients worldwide currently infected with HCV, the importance of HCV management in HCC therapeutic care and prevention is clear. The major current therapeutic goal for HCV and prevention of liver disease progression is sustained viral response (SVR), which is defined by negative HCV RNA at 12 weeks post-treatment (SVR12) and appears to be durable with a late virologic relapse rate of less than 1%. Therapeutic management of HCV has recently shifted from interferon-based therapies to all-oral interferon-free direct-acting antiviral (DAA) combination regimens. DAAs are a new class of drugs that target nonstructural proteins responsible for replication and infection of the hepatitis c virus. Genotype specific DAA therapies have been shown to reach SVR12 exceeding 90% of patients with fewer adverse effects compared with historic interferon-based regimens. SVR12 from DAA regimens have been associated with a decrease in liver outcomes including cirrhosis, hepatic decompensation, HCC and mortality. However, the impact of DAA regimens on clinical outcomes in patients with HCC remain limited. This study evaluates the impact of DAA on overall survival in HCV patients with HCC with the *a priori* hypothesis that

SVR12 would be associated with improved outcome.

Source: Scientific Reports | (2019) 9:17081 | <https://doi.org/10.1038/s41598-019-53051-2>

Combating atherosclerosis with targeted nanomedicines: recent advances and future prospective.

Cardiovascular diseases (CVDs) are recognized as the leading cause of mortality worldwide. The increasing prevalence of such disease demand novel therapeutic and diagnostic approaches to overcome associated clinical/social issues. Recent advances in nanotechnology and biological sciences have provided intriguing insights to employ targeted nanosystems (NSs) to the desired location as multifunctional system for diagnosis, imaging and therapy of various diseases, including CVDs. Nanomedicines, as novel tool for improved drug delivery, imaging, and diagnosis, have shown great promise in combating the CVDs. A cascade of biological events can result in the formation of atheromatous plaque and arterial stenosis, which need to be controlled. Recent studies have shown that nanomedicines can provide unique therapeutic benefits in the diagnosis and treatment of atherosclerosis. Despite some limitations, nanomedicines hold considerable potentials in the prevention, diagnosis, and treatment of various formidable diseases such as atherosclerosis. They offer various benefits, including maximal therapeutic effects with minimal side effects, amenable physicochemical properties such as surface modifications, and multifunctionality. Therefore, it is strongly envisioned that by the targeted drug delivery to the atherosclerotic lesions and plaque using nanomedicines, the onset and progression of CVDs can be efficiently managed in comparison with the currently used classical treatment modalities

Source: Ment Health Clin]. 2018; 8(5):235-41. DOI: 10.9740/mhc.2018.09.235.

Treatment with a new benzimidazole derivative bearing a pyrrolidine side chain overcomes sorafenib resistance in hepatocellular carcinoma.

Hepatocellular carcinoma (HCC) is a major cause of cancer-related death worldwide. Currently, sorafenib is the standard first-line drug for patients with advanced HCC.

However, long-term exposure to sorafenib often results in reduced sensitivity of tumour cells to the drug, leading to acquired resistance. Therefore, developing new compounds to treat sorafenib resistance is urgently needed. Although benzimidazole and its derivatives have been reported to exert antimicrobial and antitumour effects, the anti-drug resistance potential of these molecules is still unknown. In this study, we established sorafenib-resistant (SR) cell lines and an acquired sorafenib resistance xenograft model. We showed that treatment with a benzimidazole derivative bearing a pyrrolidine side chain (compound 9a) inhibited the proliferation of SR cells by blocking the phosphorylation of AKT, p70S6 and the downstream molecule RPS6. In addition, caspase 3/PARP-dependent apoptotic signals were induced in 9a-treated cells. Regarding epithelial-mesenchymal transition (EMT) activities, 9a treatment significantly suppressed the migration of SR cells. In particular, the levels of EMT-related transcription factors (snail, slug and twist) and mesenchymal markers (vimentin and N-cadherin) were down regulated. In the acquired sorafenib resistance xenograft model, compound 9a administration decreased the growth of tumours with acquired sorafenib resistance and the expression of the HCC markers α -fetoprotein, glypican 3 and survivin. In conclusion, treatment with this compound may be a novel therapeutic strategy for patients with sorafenib resistance.

Scientific Reports | (2019) 9:17259 | <https://doi.org/10.1038/s41598-019-53863-2>

mTOR in Down Syndrome: Role in A β and Tau Neuropathology and Transition to Alzheimer Disease-Like Dementia

The mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase involved in the regulation of protein synthesis and degradation, longevity and cytoskeletal formation. The mTOR pathway represents a key growth and survival pathway involved in several diseases such as cancer, obesity, cardiovascular disease and neurodegenerative diseases. Numerous studies linked the alterations of mTOR pathway to age-dependent cognitive decline, pathogenesis of Alzheimer disease (AD) and AD-like dementia in Down syndrome (DS). DS is the most frequent chromosomal abnormality that causes intellectual

disability. The neuropathology of AD in DS is complex and involves impaired mitochondrial function, defects in neurogenesis, increased oxidative stress, altered proteostasis and autophagy networks as a result of triplication of chromosome 21(chr 21). The chr21 gene products are considered a principal neuropathogenic moiety in DS. Several genes involved respectively in the formation of senile plaques and neurofibrillary tangles (NFT), two main pathological hallmarks of AD, are mapped on chr21. Further, in subjects with DS the activation of mTOR signaling contributes to A β generation and the formation of NFT. This review discusses recent research highlighting the complex role of mTOR associated with the presence of two hallmarks of AD pathology, senile plaques (composed mostly of fibrillar A β peptides), and NFT (composed mostly of hyperphosphorylated tau protein). Oxidative stress, associated with chr21-related A β and mitochondrial alterations, may significantly contribute to this linkage of mTOR to AD-like neuropathology in DS.

Source: Free Radic Biol Med. 2018 January ; 114: 94101..

Advances in B-cell Precursor Acute Lymphoblastic Leukemia Genomics

In childhood B-cell precursor acute lymphoblastic leukemia (BCP-ALL), cytogenetic abnormalities remain important diagnostic and prognostic tools. A number of well-established abnormalities are routinely used in risk stratification for treatment. These include highhyperdiploidy and ETV6-RUNX1 fusion, classified as good risk, while Philadelphia chromosome (Ph) positive ALL and rearrangements of the KMT2A(MLL) gene define poor risk. A poor risk subgroup of intrachromosomal amplification of chromosome 21 (iAMP21-ALL) has been described, in which intensification of therapy has greatly improved outcome. Until recently, no consistent molecular features were defined in around 30% of BCP-ALL (known as B-other-ALL). Recent studies are classifying them into distinct subgroups, some with clear potential for novel therapeutic approaches. For example, in 1 poor risk subtype, known as Ph-like/BCR-ABL1-like ALL, approximately 10% have rearrangements of ABL-class tyrosine kinases: including ABL1, ABL2, PDGFRB, PDGFRA, and CSF1R. Notably, they show a poor response to standard chemotherapy, while they respond to treatment with

tyrosine kinase inhibitors, such as imatinib. In other Ph-like-ALL patients, deregulation of the cytokine receptor, CRLF2, and JAK2 rearrangements lead to activation of the JAK-STAT signaling pathway, implicating a specific role for JAK inhibitors in their treatment. Other novel subgroups within B-other-ALL are defined by the IGH-DUX4 translocation, related to deletions of the ERG gene and a good outcome, while fusions involving ZNF384, MEF2D, and intragenic PAX5 amplification (PAX5AMP) are linked to a poor outcome. Continued genetic screening will

eventually lead to complete genomic classification of BCP-ALL and define more molecular targets for less toxic therapies.

Source: HemaSphere, 2018; 2:4. <http://dx.doi.org/10.1097/HS9.0000000000000053>

Dr. Marukh Hameed Zargar, PhD

Department of Advance Human Centre for Genetics