Fifty-eight patients had classic papillary thyroid cancer (PTC) and only 1 patient had follicular thyroid cancer. Among the patient with PTC, 39.6% (23/58) had follicular-variant PTC, 8.6% (5/52) had diffuse-sclerosing PTC and 17.2% (10/58) had other variants. Nineteen (32%), 30 (51%), and 10 (17%) had low-risk, intermediate-risk, and high-risk disease, respectively.

Within the Low-risk group, 68% (13/19) received ^{131}I. The mean initial dose was 60.9 mCi [26-150 mCi]. Eighty four percent (11/13) received ≤100 mCi and 27% (3/11) had residual/relapsed disease. Fifteen percent (2/13) received >100 mCi and none had residual/relapsed disease. Sixteen percent (1/6) of patients without ^{131}I therapy had residual/relapsed disease. (P=0.48)

Within the Intermediate-risk group, all 30 patients received ^{131}I. The mean initial dose was 97.5 mCi [27.3-215 mCi]. Sixty percent (18/30) received ≤100 mCi and 38.8% (7/18) had residual/relapsed disease. Forty percent (12/30) received >100 mCi and 16.6 % (2/12) had residual/relapsed disease. (P=0.15)

Within the High-risk group all 10 patients received ^{131}I. The mean initial dose was 159.9 mCi [129.3-384 mCi]. Fifty percent (5/10) received ≤150 mCi and 60% (3/5) had residual/relapsed disease. Fifty percent (5/5) received >150 mCi and 20% (1/5) had residual/relapsed disease. (P=0.2)

Conclusion: There are no statistical differences of disease-free rate between the initial dose of ^{131}I among all risk categories. However, the use of more than 100 mCi in the intermediate-risk category and more than 150 mCi in the high-risk category may be recommended.

Tumor Biology

TUMOR BIOLOGY: DIAGNOSTICS, THERAPIES, ENDOCRINE NEOPLASIAS, AND HORMONE DEPENDENT TUMORS

Translational Feasibility of Steroidogenic Factor-1 Antagonists as a Novel Targeted Therapy for Adrenocortical Cancer

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SUN-LB23

Adrenocortical carcinoma (ACC) is an aggressive cancer with devastating outcomes. ACC is usually locally advanced or metastatic at diagnosis and, despite tumor resection plus chemotherapy, has a high rate of recurrence. The 5-year survival rate among metastatic ACC patients is less than 15%. ACC responds poorly to the single FDA-approved drug, mitotane, which is non-specifically adrenolytic and highly toxic. Other chemotherapy regimens tested have been unsuccessful in improving overall survival. Steroidogenic factor-1 (SF-1 or NR5A1) is an orphan nuclear receptor essential for growth and development of the adrenal gland and is the major, active transcription factor in ACC (1,2). To address the need for a targeted therapy in ACC, we have identified potent small molecule SF-1 antagonists that block SF-1 transcriptional activity through the ligand-binding domain (IC50 = 15-20 nM in a CHO cell reporter assay). In short-term dissociated cell cultures established from SJ-ACC3 (3), a pediatric ACC patient-derived tumor xenograft (PDX), the SF-1 antagonists OR-907S and OR-070 blocked DNA synthesis as measured by inhibition of EdU incorporation in SF-1+ cells (IC50 = 500-600 nM, >80% efficacy at 10 μM) whereas OR-907R, the 100-fold less potent enantiomer of OR-907S, is nearly inactive. Because the SF-1 antagonist sensitivity of the dissociated SJ-ACC3 cells declines markedly with repeated passage of the PDX in immunocompromised (C.B-17 SCID) mice, we have utilized an alternative model system for evaluating tumor target engagement and growth inhibition: the rat Leydig tumor cell line (R2C), which is growth-inhibited by the SF-1 antagonists OR-907S and OR-070 in vitro (IC50 = 60-100 nM) and as a xenograft in immunocompromised mice (CD-1 nude). The SF-1-responsive gene signature identified by RNAseq in R2C cell cultures by comparison of OR-907S and OR-907R was replicated by OR-070 and other orally-bioavailable lead antagonists in R2C xenografts following 3 days of dosing, indicating engagement of SF-1 by these compounds. Significantly, R2C tumors were growth-inhibited following daily oral dosing for 4 weeks with OR-070 (10-30 mg/kg). These findings suggest that SF-1 antagonists could be a targeted therapy for ACC. OR-070 has >30% oral bioavailability in rat and dog, indicating that this structural class of SF-1 antagonists has potential for clinical development.References: (1) Mohan, et al., Curr. Opin. Endocrinol. Metab. Res., 2019; 8:72; (2) Corces, et al., Science, 2018; 362:eaav1898; (3) Pinto, et al., Clin. Cancer. Res., 2013; 19:1740.

Adipose Tissue, Appetite, and Obesity

ADIPOSE TISSUE BIOLOGY AND OBESITY

Loss of GLP-2R Signaling Activates Hepatic Stellate Cells and Exacerbates Diet-Induced Steatohepatitis in Mice

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SAT-LB101

A GLP-2 analogue is used in individuals with intestinal failure at risk for liver disease, yet the hepatic actions of GLP-2 are not understood. Treatment of high fat diet (HFD)-fed mice with GLP-2 did not modify the development of hepatosteatosis or hepatic inflammation. In contrast, *Glp2r*$^{-/-}$ mice exhibited increased hepatic lipid accumulation, deterioration in glucose tolerance, and upregulation of biomarkers of hepatic inflammation. Both mouse and human liver expressed the canonical GLP-2R, and hepatic *Glp2r* expression was upregulated in mice with hepatosteatosis. Cell fractionation localized the *Glp2r* to hepatic stellate cells (HSC), and markers of HSC activation and fibrosis were increased in livers from *Glp2r*$^{-/-}$ mice. Moreover, GLP-2 directly modulated gene expression in isolated HSCs ex vivo. Taken together, these findings define an essential role for the GLP-2R in hepatic adaptation to nutrient excess and unveil a gut hormone-HSC axis, linking GLP-2R signaling to control of hepatic stellate cell activation.