tumors, multinodular goiter (MNG) and differentiated thyroid cancer (DTC). MNG is very common in patients with *DICER1* Syndrome but data on incidence is lacking. MNG is more common in females than males.
Case presentation:
22 year old man who originally presented with pleuropulmonary blastoma, Type 3 at 3 years of age. His treatment included pulmonectomy, radiation of 46.6 Gy to thorax, and alkylating agents including Cisplatin, Ifosphamide and Cytoxan. He developed frontal lobe metastasis over the course of 3 years and was treated with focal cranial radiation. His father and maternal uncle had history of lung cancer.
He was evaluated at the Endocrine clinic at 12 years 10 months for short stature. His height was 132.5 cm (SDS -2.96), weight 29.7 kg (SDS -2.40), and BMI 16.99kg/m² (SDS -0.61). On examination he had normal thyroid exam and Tanner 2 bilateral 4 cc testicles. He was treated with Levothyroxine for subclinical hypothyroidism (TSH: 5.96 uIU/ml (0.35–5.5) and Free T 4: 0.99 ng/dl (0.8–1.80) and growth hormone (GH) for growth hormone deficiency (peak GH was 7.7 ng/ml after Arginine and Clonidine GH stimulation test). At 14 years 10 month he developed respiratory distress. CT scan of chest showed right lower pole nodule 1.6 x 1.5 x 1.4 cm. Ultrasound of thyroid showed right thyroid solid mid pole isoechoic nodule 1.4 x 1.7 x 1.3 cm with multiple enlarged bilateral cervical nodes, largest left supraclavicular region > 1 cm. Biopsy of the right nodule was negative for malignancy. Over the course of 2 years he developed new right thyroid isoechoic nodule in the lower pole 2.1 x 2.5 x 1.9 cm and new left thyroid isoechoic nodule in the upper pole 1.0 x 0.5 x 0.5 cm. Biopsy was negative for malignancy. Due to his PPB, MNG and family history of lung cancer he was evaluated at our genetic cancer clinic and tested positive for germline *DICER1* pathogenic variant *c.4605_4606del (p.Cys1535Trpfs*3)*
Conclusion:
Our 22 year old male presented with pleuropulmonary blastoma and over the course of few years developed MNG. Genetic testing was positive for germline *DICER1* pathogenic variant *c.4605_4606del (p.Cys1535Trpfs*3).* Our case illustrates the importance of consideration of: 1) Testing children with PPB for *DICER1* Syndrome as there are screening recommendations including regular thyroid ultrasound and examinations to look for MNG or other features concerning for thyroid gland neoplasia. 2) MNG is uncommon in children and detection of this should raise suspicion for consideration of testing for *DICER1* Syndrome.

Cardiovascular Endocrinology

ENDOCRINE HYPERTENSION AND ALDOSTERONE EXCESS

Effects of Mineralocorticoid Receptor Antagonists on Primary Aldosteronism Screening

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SAT-561

Background: Mineralocorticoid receptor antagonists (MRAs) are the mainstay of medical therapy for primary aldosteronism (PA), and MRAs also benefit patients with other forms of resistant hypertension and cardiovascular disorders. MRAs impact the renin-angiotensin-aldosterone system (RAAS), raising concerns regarding the accuracy of PA screening. The rate of false negative and/or false positive screening for PA in patients taking MRAs has not been systematically evaluated. Herein, we assessed the alterations of both renin and aldosterone after MRA initiation in a large cohort of patients with hypertension.
Patients and Methods: We conducted a retrospective cohort study of patients with hypertension seen in a tertiary referral center. We employed our center's database search engine to identify adults with hypertension who were treated with MRAs. Of these, we included patients who had renin and aldosterone measured both before and after MRA treatment. We excluded patients with adrenal cortical cancer, end-stage renal disease, exogenous glucocorticoids, and critically ill. PA screening was considered positive when plasma aldosterone concentration (PAC) was 10 ng/dL, plasma renin activity (PRA) was 1.0 ng/mL/h, and the aldosterone-to renin ratio (ARR) was 20. Mann-Whitney test and Wilcoxon signed rank test were employed to compare independent or paired groups, respectively.
Results: In total, 109 patients (57 women), mean age 55+/-13 years were included. Of these, 40% had confirmed PA (14% unilateral and 26% bilateral); in 38% PA was excluded; and in the remaining 22%, testing for PA was incomplete. On average, patients were on 3 +/- 1.6 antihypertensive agents; 60% of patients were prescribed beta blockers, 49% K^+-wasting diuretics and 35% were on K^+ supplements. Both PAC and PRA increased after MRA treatment (from 19.0 [12.6, 26.7] to 26.3 [17.2, 36.2]; and from 0.6 [0.10, 0.80] to 1.00 [0.60, 2.80], respectively, $p < 0.0001$ for both), while ARR decreased from 42.5 [18.5, 109.8] to 24.0 [10.9, 55.5] ($p = 0.003$). Of 71 patients with positive PA screening at baseline, 31 (43.7 %) no longer met positive screening criteria during MRA therapy. Conversely, 7 of 38 patients (18 %) with negative screening at baseline met criteria for positive PA screening while on MRA treatment, including 5 patients with a PAC > 20 ng/dL along with suppressed renin. The impact on PA screening accuracy remained similar irrespective of the MRA dose, duration of treatment, changes in concomitant antihypertensive drugs, or hypertension type.
Conclusions: Commonly, MRA treatment leads to renin elevation, ARR reduction, and consequential false negative PA screening. In a minority of patients, MRA therapy can be followed by aldosterone elevations asynchronous from renin, possibly via short feedback loops, mimicking PA. Whenever possible, PA testing should be conducted after MRA discontinuation.

Steroid Hormones and Receptors

STEROID AND NUCLEAR RECEPTORS

Full Antagonism of Breast Cancer Cell Proliferation Can Result from Many Ligand-Induced Conformational Distortions of the Estrogen Receptor Ligand Binding Domain

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OR12-07

Although most estrogen receptor alpha (ERα)-positive breast cancers initially respond well to endocrine therapies using aromatase inhibitors (AIs) or antiestrogens, after varying time periods the cancer frequently recurs as metastatic disease. A significant fraction of these recurrences are driven by ERs that have acquired activating mutations in their ligand binding domains (LBDs), giving them constitutive activity and thus resistance to AIs. Because these mutations also reduce the affinity and potency of SERMs and SERDs, expanded efforts have been made to vary the structure of antiestrogens to make them more potent.

Typical antiestrogens are comprised of a core element that binds securely in the ligand binding pocket and from which extends a single ring (ring E) having a side chain that sterically interferes with the position of helix-12 by direct antagonism, reorienting it so that it occludes the activation function 2 (AF2) hydrophobic groove for coactivator binding. Through structural studies, we found that bridged oxabicycloheptene-sulfonamide (OBHS-N) core ligands have two rings (E and F) that can be poised to engage in both "direct antagonism" and "indirect antagonism", the latter of which disrupts the orientation of helix-12 by impinging on helix-11 and the helix-11–12 loop.

In this study, we have placed typical antiestrogen side chains on either the E or the F ring of OBHS-N core ligands and characterized their activities in ERα-positive breast cancer cells. All compounds have full antiproliferative activity and reverse estrogen-regulated gene expression, with the antiproliferative potency of each type of side chain having a distinct preference for E- vs F-ring attachment. Conformational analysis using a multiplexed coregulator peptide interaction assay shows that compounds with an E-ring substitution have interaction profiles similar to 4-hydroxytamoxifen and fulvestrant, whereas the F-ring substitution gives a very different pattern, suggesting that the antagonist activity of the two classes rely on different sets of coregulator proteins. A large number of high resolution (better than 2 Å) X-ray crystal structures reveal that this set of novel ER antagonists disrupt the conformation of the ER LBD in a variety of ways, several of which are distinct from those seen with previous antiestrogens such as Tamoxifen and Fulvestrant.

Our findings expand design concepts by which ERα ligands can block the activity of this receptor and illustrate how direct and indirect modes of ER antagonism can be combined to facilitate the development of more efficacious antiestrogens for breast cancer treatment and possibly for regulating ER-mediated activities in other estrogen target tissues.

Adrenal

PROGRESS IN ADRENAL CORTEX AND MEDULLA RESEARCH

Effects Of Alpha-emitting Meta-^{211}At-astato-benzylguanidine (^{211}At-MABG) Compared To ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) on Tumor Growth Suppression in a Pheochromocytoma Mouse Model

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OR03-01

Objectives: Given the limited treatment approaches currently available for patients with metastatic pheochromocytoma and paraganglioma (PPGL), new effective approaches are being sought. The radioisotope approach using ^{131}I-meta-iodobenzylguanidine (^{131}I-MIBG) has limited survival benefits in metastatic PPGL but is currently considered one of the standard therapeutic approaches. In theory, the alpha-emitting radiopharmaceutical *meta*-^{211}At-astato-benzylguanidine (^{211}At-MABG) could be a very effective targeted treatment for metastatic PPGL. However, this possibility has not been evaluated. Therefore, the purpose of this study was to evaluate the tumor growth suppression effects of ^{211}At-MABG compared to ^{131}I-MIBG using a PC-12 mouse pheochromocytoma model.

Methods: Rat pheochromocytoma (PC-12) cells were subcutaneously inoculated into male BALB/c nu/nu nude mice. When tumor volumes reached approximately 300 mm^3, mice bearing PC-12 tumors received intravenously either 1.11 MBq of ^{211}At-MABG (n=6), 31 MBq of ^{131}I-MIBG (n=3) or vehicle solvent (n = 6). The tumor volume was measured 3 times per week for 2 weeks. The tumor volume was compared among the three groups.

Results: At 14 days, the tumor volumes significantly increased in the control group (328.82±83.65 to 3568.83±693.23 mm^3, P<0.001). In contrast, there were no significant changes in tumor volumes in the ^{211}At-MABG group (284.65±56.77 to 274.3±87.95 mm^3, P=0.616) and ^{131}I-MIBG group (484.40±46.25 to 323.93±127.27 mm^3, P=0.084). The ^{211}At-MABG group showed significantly lower percentage change in tumor volume than did the control group (-5.0±15.99 vs. 1043.83±320.79%, P<0.001), and ^{131}I-MIBG group also showed significant volume reduction rate compared to that of the control group (-34.33±21.39 vs. 1043.82±320.79%, P<0.001). There was no significant difference in percentage tumor volume changes between the ^{211}At-MABG and ^{131}I-MIBG groups (P=0.052). **Conclusion:** At 14 days after radiopharmaceutical administration, ^{211}At-MABG produced significant tumor volume reduction as compared to that in the control group and to that associated with ^{131}I-MIBG, which is considered one of the current treatment options. Therefore, ^{211}At-MABG may have future clinical applications for the treatment of metastatic pheochromocytoma and paraganglioma.