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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.