Severe PI3Kinase Overgrowth Syndrome Treated with the AKT Inhibitor Miransertib

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Background

- Somatic activating mutations in phosphatidylinositol 3-kinase (PI3K) and serine-threonine protein kinase (AKT1) have been shown to cause abnormal segmental overgrowth phenotypes.

- Miransertib (ARQ 092) is a novel highly selective oral AKT inhibitor with a proven in-vitro efficacy. Its potential as a therapeutic option for overgrowth patients who have exhausted conventional treatment methods was investigated through the assessment of longitudinal MRI data acquired from one patient between 12/2015 and 04/2018 with the treatment started in 06/2016.

Case Report

- A term baby girl born to non-consanguineous parents had a large posterior thoracic wall lipoma and large feet with splayed toes at birth. Progressive lipomatous overgrowth and leg length discrepancy were treated with repeated surgical procedures during the first ten years of her life. Despite this the progressive replacement of normal tissues with fatty overgrowth resulted in severe subcutaneous, intra-abdominal and paraspinal involvement causing obstructive uropathy with bladder displacement and neuropathic bladder dysfunction, impaired mobility and dysfunctional sitting and lying posture associated with pain.

- By age 13 the patient was wheelchair bound and had a suprapubic catheter inserted to relieve obstructive uropathy leading to frequent hospitalisations with urinary tract infections. mTOR inhibitor sirolimus was commenced age 15 but discontinued after 12 months of therapy due to progression of the disease.

- The patient was unable to lie flat at this stage due to respiratory compromise caused by extreme diaphragm elevation by intraabdominal lipomatous overgrowth as well as flank pain caused by massive lipomatous distension.

- Surgical remedy was deemed impossible due to the infiltrative nature of fatty overgrowth encasing vital structures in the patient’s retroperitoneum. Cellular studies indicated high levels of AKT activation in fibroblasts from the affected areas.

- ARQ 092 was commenced on a compassionate basis at a dose of 30 mg daily. The patient experienced improvement in her respiratory compromise.

Results and Conclusion

- Serial volumetric DIXON MRI analysis was carried out by a radiologist defining regions of interest (ROI) on slices of the in-phase images to define areas of fatty overgrowth using Dynamika software as a platform for imaging data analysis.

- Calculated volumes of fatty overgrowth declined by approximately 15% after treatment commenced.

- The patient has now completed 25 months of therapy with clinically stable disease and clear radiological improvement.

- Miransertib was well tolerated with no significant toxicities other than hyperlipidaemia comparable to lipid profile derangement previously noted on sirolimus therapy.