Therapeutic Targeting of IDH1 Mutations in Intrahepatic Cholangiocarcinoma Arising in Ollier Disease

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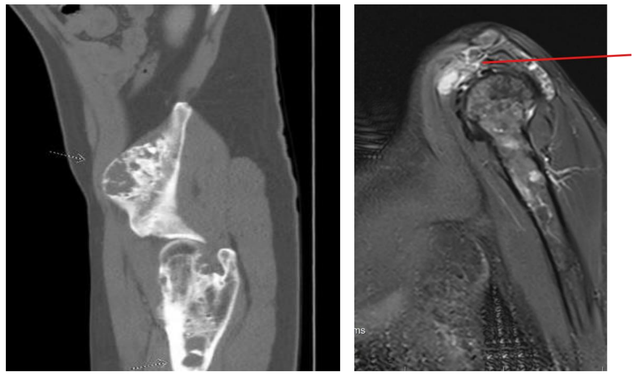
Background:

- Ollier disease: rare, non-hereditary skeletal disorder characterized by multiple enchondromas and somatic *IDH1* mutations
- Prevalence: ~1 in 100,000, typical onset in childhood before age 10
- Associated with increased malignancy risk, particularly chondrosarcoma, also at increased risk for intrahepatic cholangiocarcinoma (iCCA)
- Enchondromas are benign, intramedullary cartilaginous tumors in bone; typically are asymmetric and variable in size, shape and location, usually painless unless malignant transformation/fracture
- *IDH1* mutations are seen in ~20% of sporadic iCCA, however no report exists for IDH1-targeting in Ollier disease with iCCA

Methods:

- Retrospective study of three patients with Ollier disease who developed IDH1-mutated iCCA
- Clinical, histopathologic, and molecular data were reviewed
- Treatment regimens, including use of ivosidenib, a selective IDH1inhibitor, and associated outcomes were analyzed

Figure 1: Differentiating Enchondroma, Chondrosarcoma or Bone Metastasis



Pelvic and femoral enchondromas on the left compared to coracoid process bony metastasis on the right. Enchondromas and especially chondrosarcomas can present similarly radiographically to bony metastases. Enchondromas typically present as well-defined lytic, slightly expansile lesions usually with internal calcification and endosteal thinning with “ring and arc” pattern.

Results/Graphs/Data:

- Age of diagnosis was between ages 25–45, notably younger than the typical median age of 67
- Histopathology for all patient showed moderately-poorly differentiated adenocarcinoma with dense desmoplastic stroma
- Enchondromas presented as calcified expansile lesions that could mimic bony metastases based on radiographic appearance
- Prior platinum-based chemotherapy was used in all cases, ivosidenib was administered either as monotherapy or in combination with cytotoxic agents (FOLFOX or gemcitabine/cisplatin)
- PFS on ivosidenib was 3-7 months, consistent with ClarIDHy trial results
- Ivosidenib was well tolerated, with no unexpected adverse events

Table 1: Patient Characteristics, Mutational Profile, Treatments, and Outcome Measures

Patient	Age at Diagnosis	Sex	Stage at Diagnosis	Mutations	Surgery, Radiation or Localized Therapy	Previous systemic treatments	Concurrent systemic treatment with Ivosidenib	PFS on Ivosidenib (months)	OS (months)
1	45	F	IIIB	IDH1 R132C, TP53, POLE	Left extended hepatectomy; Radiation to liver + bony metastases	Capecitabine; Gemcitabine + Cisplatin + Durvalumab	FOLFOX	3	16
2	28	F	IV	IDH1 R132C, NRAS, PIK3CA, RB1	No	Gemcitabine + Cisplatin	Gemcitabine + Cisplatin	7	14
3	25	M	IIIB	IDH1 R132C, ARID2, ASXL1, FH	Y90 embolization x2	Gemcitabine + Cisplatin + Nab-paclitaxel; Gemcitabine + Cisplatin + Durvalumab	N/A	3	26

Conclusions/Future Directions

- Our findings support the feasibility and tolerability of ivosidenib in Ollier disease with comparable efficacy to sporadic IDH1-mutant iCCA
- Desmoplastic histology and early onset may be distinguishing features
- Notably, enchondromas and/or chondrosarcomas may mimic bone metastases radiographically, posing diagnostic challenges
- A case report by Funck-Brentano et al. for a patient with Maffucci syndrome (somatic *IDH1* mutation, enchondromas and hemangiomas) with *IDH1*-mutated glioma showed clinical stability of glioma on ivosidenib – interestingly with improvement of symptoms related to enchondromas and radiographic evidence of new bone formation; there may be a role for disease-modifying therapy with *IDH1*-targeting therapy

Background:

- Ollier disease is a rare genetic disorder characterized by underlying gene mutation (usually *IDH1*) which leads to benign bone growths and predisposes to cancers, including chondrosarcoma and iCCA
- Ivosidenib, an IDH1 inhibiting therapy approved for treatment of previously treated IDH-1 CCA has not been studied in Ollier patients

Methods:

- This study reviewed three patients with Ollier disease treated with Ivosidenib to assess treatment response
- Clinical, histopathologic and molecular data were reviewed

Results/Conclusion:

- Patients developed iCCA at younger age than general population
- Ivosidenib was well-tolerated and median progression-free survival was similar to that of non-Ollier IDH-1 mutated CCA
- Differentiating bone lesions due to Ollier disease from malignant transformation or bone metastases can be challenging through imaging
- A case report for a patient with similar genetic disorder, Maffucci syndrome, with *IDH1*-mutated glioma showed promise in symptoms related to bone lesions – this suggests the possibility of ivosidenib as disease modifying therapy in Ollier disease

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