Treatment of gestational trophoblastic neoplasia and choriocarcinoma by targeting the endoglin-BMP-9 axis

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BACKGROUND

Although most patients with low-risk gestational trophoblastic neoplasia (GTN) will be cured with methotrexate (MTX), 10-50% of patients will develop drug resistance1. Currently, there is no means to predict which patients with low risk GTN will develop MTX resistance and require multi-agent therapy. In addition, while etoposide-based multi-agent regimens remain the standard for first line therapy for patients with high risk GTN or for second line therapy for patients failing single agent treatments, there are limited therapeutic options for patients resistant to etoposide, and patients continue to succumb from this disease2.

Endoglin (CD105) is a 663 amino acid, 180 kDa homodimer that acts as an auxiliary membrane cofactor of TGFβ receptors. Endoglin controls VEGF signaling through FLK1 by modulating the balance between two different SMAD signaling pathways:

- BMP9/ALK1/p53AD1/5/8
- TGFβ/ALK5/pSMAD2/3

Previous studies have shown that endoglin plays an important role in the pathogenesis of preeclampsia. For this study, we hypothesized that endoglin might also have a part in the development of another placental disease, gestational trophoblastic neoplasia.

AIMS

1. Investigate endoglin expression in in vitro models
2. Assess the potential for endoglin or its ligand BMP-9 to serve as biomarkers for chemoresistance in vivo
3. Explore the potential endoglin targeted therapy to treat chemoresistant choriocarcinoma.

MATERIALS AND METHODS

1) Expression of endoglin in trophoblast cell lines using qRT-PCR, Western blots, and ELISA
2) IHC to correlate endoglin and BMP-9 expression in a tissue microarray containing 22 complete moles
3) Case control study of serum endoglin and BMP-9 in 76 patients with low risk GTN post-complete mole
4) Single patient clinical trial of TRC105, an investigational compound targeting Endoglin

RESULTS – In vitro

- Fig. 1 Endoglin function

Endoglin is highly expressed in syncytiotrophoblasts and GTN, and its expression is induced by methotrexate. Serum BMP9, the ligand for endoglin, may be a useful marker for increased endoglin activity and subsequent methotrexate resistance in patients with GTN. In the first case of endoglin-targeted therapy for choriocarcinoma, we report a complete clinical response in a highly pretreated patient who had exhausted all other lines of therapy.

REFERENCES