Histologic Diversity of Thymic Epithelial Tumors in Patients with Myasthenia Gravis

Heldman EM, Davis HO, Laniak LJ, Wuthrich BS, Loehrer PJ, Kesler KA

Background and Objective: Thymic epithelial tumors (TETs) include thymic carcinomas and thymomas, the latter of which can be further categorized by the World Health Organization (WHO) histologic classification based on the morphology of epithelial cells and the ratio of lymphocyte to epithelial cells (WHO types A, AB, B1, B2, and B3). TETs are rare malignancies with an incidence of 0.15 per 100,000 person-years in the United States. While their etiologies remain unknown, these tumors are associated with distinctly high rates of autoimmune disorders and paraneoplastic syndromes. The most common comorbid autoimmune disorder is myasthenia gravis (MG), affecting approximately 30% of patients with thymoma; thus, evaluating the risk of MG in patients with TETs of various histologies is important clinically. For the present retrospective study, we created a database of patients with TETs and examined prevalence of each histologic subtype in patients with MG.

Methods: Drs. Patrick Loehrer, Kenneth Kesler, and colleagues have collaborated at the Indiana University Simon Cancer Center to care for over 1000 patients with TETs. The electronic health records of these patients were accessed via Cerner and used to input demographic, diagnostic, and histologic data into a REDCap database. The TETs were further categorized by WHO classification, and heterogenous tumors were categorized by their most aggressive histologic type (i.e. mixed type B2 and B3 categorized as B3).

Results: Of 1023 total patients in the REDCap database, 626 were found to have sufficient documented information regarding TET diagnosis and histology as well as the presence or absence of MG (thymoma – 468; thymic carcinoma – 158). 112 of these patients carried diagnoses of both MG and a TET confirmed by pathology report (thymoma – 110; thymic carcinoma – 2). 77 (68.75%) patients were diagnosed with MG prior to TET, while 30 (26.79%) were diagnosed with MG after TET ($p < 0.0001$). The greatest prevalence of WHO histologic type in patients with thymoma and MG was Type B3 (36, 32.14%), followed by Type B2 (33, 29.46%), Type B1 (19, 16.96%), Type A (7, 6.25%), and Type AB (7, 6.25%) ($X2 = 37.41$, $p < 0.0001$). Notably, only 2 of 158 (1.27%) total patients with TC had comorbid MG in contrast to 110 of 468 (23.50%) with thymoma and MG; this suggests a uniquely favorable microenvironment of thymoma in patients with MG.

Clinical Impact and Implications: A distinct link exists between myasthenia gravis and thymoma, particularly those of more aggressive WHO histologic types (Type B3 and Type B2). Future work will aim to determine whether histologic classification has a predictive value for tumor prognosis in patients with and without MG. Furthermore, patterns of gene expression associated with thymoma in patients with and without MG may elucidate the etiologic mechanisms for the development of this autoimmune disorder.

William H. and Fern L. Hardiman Scholarship

Targeted Inhibition of the HGF/c-Met Pathway by Merestinib Augments the Effects of Albumin-Bound Paclitaxel in Gastric Cancer

Kaurich Q, Huang J, Awasthi N

Introduction: Combination chemotherapy regimens are commonly used to treat gastric adenocarcinoma (GAC), but the median survival time remains less than one year. Nab-paclitaxel has demonstrated high antitumor activity in previous GAC studies. Many growth factors and their receptors are overexpressed in GAC and have been implicated in its pathophysiology. We hypothesize that merestinib, a small-molecule inhibitor targeting c-Met, Axl, and DDR1/2 pathways, will have significant antitumor effects and will enhance the response to nab-paclitaxel in GAC preclinical models.

Methods: In vitro proliferation and protein expression were assessed using WST-1 and immunoblot assays. Subcutaneous xenografts of MKN-45 and SNU-1 cell lines were implanted in mice to study tumor growth inhibition. Immunohistochemistry was performed to examine intratumor proliferation and microvessel density.

Results: In vitro assays showed that nab-paclitaxel and merestinib decreased cell proliferation in all three cell lines, with an additive effect in combination. Reduction in cell proliferation at low doses of nab-paclitaxel (10 nM), merestinib (100 nM), and their combination was 87%, 82%, and 94% (MKN-45 cell line, high phospho-c-Met expression), 59%, 50%, and 82% (SNU-1 cell line, low phospho-c-Met expression), and 53%, 19%, and 66% in gastric fibroblasts. Immunoblot analysis of merestinib treated MKN-45 cells revealed increased expression of apoptotic proteins and decreased expression of phospho-c-Met, phospho-EGFR, phospho-IGF-1R, phospho-ERK, and phospho-AKT. In gastric fibroblasts, merestinib decreased phospho-ERK and increased apoptotic protein expression. Phospho-c-Met and phospho-EGFR were not detected in SNU-1 immunoblots; however, phospho-ERK, phospho-VEGFR, and apoptotic protein expression increased after treatment. In MKN-45 xenografts, net tumor growth in control, nab-paclitaxel, merestinib, and combination groups was 503 mm3, 115 mm3, 91 mm3, and -9.7 mm3. Immunohistochemistry analysis of tumor cell proliferation and microvessel density corroborated tumor growth study results.

Conclusion: The data suggest that merestinib in combination with nab-paclitaxel carry a promising potential for improving clinical GAC therapy.

William H. and Fern L. Hardiman Scholarship

Quinn Kaurich is a third-year medical student, who is currently interested in internal medicine.

"My most important takeaway from my research is the realization that preclinical research plays a critical role in the biomedical research process. Although it is not always easy to see its connection to benefiting real patients, it is a necessary step in the process. Preclinical research is also exciting because it gives us the opportunity to try out new things without the fear of causing any harm. I am extremely grateful for the opportunity to contribute to the field of targeted cancer therapy, and I am hopeful that this work may one day help people with gastric cancer."