Abstracts

IMMUNOLOGY/IMMUNOTHERAPY

IM-01. ANTI-TUMOR EFFECT OF TRASTUZUMAB, GM-CSF AND IL-2 COMBINATORIAL THERAPY IN PEDIATRIC EPENDYOMA
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We have previously shown that (i) the amount of tumor-infiltrating microglia/macrophage (M/M) in pediatric brain tumor ependymoma (EPN) is positively correlated with survival and (ii) identified an immunosuppressive phenotype in poor prognosis subgroup A of EPN. These data support the development of immunotherapy for EPN, a tumor in which approximately 50% of patients suffer recurrence and for which chemotheraphy has not yet shown any benefit. In these preclinical and clinical studies we evaluated the combination of therapeutic antibody trastuzumab, GM-CSF and IL2 for the treatment of EPN. Transcriptomic analysis identified ERBB2, targetable by therapeutic antibody trastuzumab, as overexpressed in EPN. Flow cytometric analysis showed that trastuzumab was bound to ErbB2-expressing EPN tumor and infiltrating M/M. Tumor infiltrating M/M express high levels of high-affinity Fc-gamma receptor CD64 which we suspect are binding the Fc of trastuzumab. Allogeneic and autologous EPN cell line immune cell co-cultures demonstrated significantly increased ADCC with combined trastuzumab and GM-CSF. Primary human EPN organotypic culture studies demonstrated decreased tumor proliferation and increased immune cell proliferation in response to combined trastuzumab, GM-CSF and IL2. To date we have recruited 4 patients to the first pilot clinical study of GM-CSF delivered prior to surgery in children with relapsed EPN. Transcriptomic analysis of post-treatment tumor samples demonstrated that GM-CSF upregulated antigen processing and presentation genes, a hallmark of an activated immunophenotype. These results demonstrate that combined trastuzumab/GM-CSF/IL2 is effective at not only priming the newly recruited immune cells to target the tumor but may also reverse the immunosuppressive phenotype. The potential of complementary combinatorial immunotherapeutic regimens in EPN warrants expedited investigation.