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Antitumor Efficacy of Anti-PDL-1 In ACTH-secreting Pituitary Adenomas: A Novel Immunotherapeutic Approach For Cushing's Disease

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Introduction

Cushing's disease (CD), caused by ACTH-secreting pituitary adenomas, is a highly morbid condition with few treatment options beyond surgery and radiotherapy. Furthermore 25% of patients prove refractory to standard of care. We and our collaborators recently reported expression of PDL-1 on human pituitary adenomas, providing a viable and novel immunotherapeutic target. Here we test anti-PDL-1 in vivo in a recapitulative murine model of CD.

Methods

PDL-1 on human ACTH-secreting adenomas was further assessed via IHC. The murine ACTH-secreting ATT20/D16v.2 adenoma cell line was utilized to establish subcutaneous and intracranial models of CD in syngeneic A/HeJ x C57L/J F1 or nude athymic mice. Tumor PDL-1 was assessed by flow cytometry and IHC. Plasma ACTH was measured by ELISA in subcutaneous models. Mice were treated intraperitoneally with anti-PDL1 or isotype every 3 days x 12 doses. For subcutaneous tumors, tumor volume and plasma ACTH were assessed, while survival was evaluated in the intracranial model. Tumor-infiltrating lymphocytes (TILs) were harvested and analyzed by flow cytometry.

Results

Human pituitary adenomas demonstrate significant (>1% staining) PD-L1 expression in 32% of samples, including 22% of ACTH-secreting adenomas. Murine ATT20/D16v.2 tumors also demonstrate elevated PD-L1 expression, as well as elevated plasma ACTH, recapitulating CD. Anti-PDL1 treated mice demonstrated reductions to tumor volume (p=0.0069, unpaired t test) in the subcutaneous model as well as long term survival in the intracranial model. TILs in treated mice expressed lower levels of the exhaustion markers PD-1, TIM-3, and LAG-3. Accordingly, anti-PDL-1 efficacy was lost in athymic mice, revealing a T-cell-dependent treatment benefit.

Conclusions

PDL-1 is significantly elevated on ACTH-secreting pituitary adenomas in patients and mice, yielding a significant T-cell dependent antitumor effect to treatment with anti-PDL1. These results demonstrate an appropriate murine model for pre-clinical investigation and a promising immunotherapeutic approach for CD. A multi-institution clinical trial is planned.

Learning Objectives

By the conclusion of this session, participants should be able to: 1) Discuss the importance of exploring further therapeutic options for patients with refractory Cushing's Disease, 2) Discuss, in small groups, the rise and role of immunotherapies in treating intracranial cancers, 3) Identify the possible role of anti-PDL1 therapy for refractory Cushing's Disease

References

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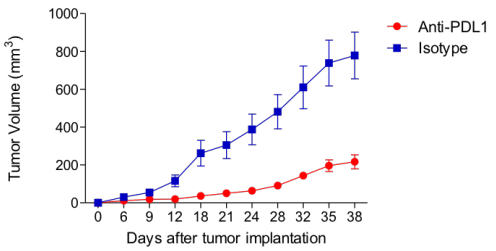
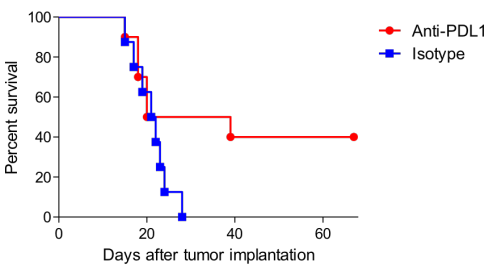
Tumor Volume Reduction in SC model



In vivo anti-tumor efficacy in mice bearing subcutaneous pituitary adenoma tumors.

Survival Curve in IC model



In vivo anti-tumor efficacy in mice bearing intracranial pituitary adenoma tumors.

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