Identifying Synergistic Combinations with CDK 4/6 Inhibitor Palbociclib for H3K27M Diffuse Intrinsic Pontine Glioma

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Purpose

This study examines the benefits of combining a CDK4/6 inhibitor with existing epigenetic therapies for the treatment of diffuse intrinsic pontine glioma (DIPG).

Background & Significance

- DIPG remains a devastating diagnosis for pediatric populations with an expected 5-year survival below 1%.
- Recent studies demonstrate that palbociclib, an orally active CDK4/6 inhibitor, inhibits cell growth in vitro by preventing phosphorylation of Rb and targeting cell cycle dysregulation in DIPG.
- Several epigenetic therapies, including histone deacetylase inhibitors (HDAC), counteract tumor growth by inhibiting the dysregulated transcription in the > 80% of DIPG cases harboring an H3K27M mutation.
- Systemic toxicities, such as neutropenia, limit effective dosing for both of these therapeutic strategies independently. This is attributable, in large part, to dose-escalation due to poor CNS penetrance.
- However, it remains unclear whether combination therapy utilizing both palbociclib and epigenetic therapies for DIPG could produce synergistic growth inhibition of DIPG and therefore lower the dosing required for treatment.

Methods

- A literature review of promising epigenetic targets for H3K27M-mutant DIPG identified 3 candidate compounds as potential synergistic partners with palbociclib.
- Single-compound validation was conducted using 72-hour post-administration luminescence cell viability assays in 4 well-established DIPG cell lines harboring H3K27M mutations (DIPG-IV, SF8628, DIPG-XIII, and DIPG-XVII).
- Cell viability assays for combination therapy were conducted using DIPG-XIII and DIPG-XVII cell lines.
- Combination indices were obtained via the Chou-Talalay method to assess synergy, where CI values < 1, = 1, and > 1 indicate synergism, additive effects, and antagonism, respectively.

Results of Monotherapy Screening

- Palbociclib monotherapy demonstrated in vitro growth inhibition of all 4 DIPG cell lines (GI50 range: 2.33-6.01μM) at micromolar doses, similar to previous reports in the literature.
- All 3 epigenetic therapies demonstrated therapeutic efficacy in micromolar or nanomolar ranges across all 4 DIPG cell lines tested.

- These compounds were the HDAC inhibitor panobinostat, the histone deacetylase inhibitor GSK-J4, and the BET protein inhibitor JQ1. Although, effective growth inhibition after administration of JQ1 was only reliably produced in DIPG-XVII and DIPG-XIII cell lines.

Palbociclib & GSKJ4 Combination Therapy

- Combination screening of GSKJ4 with palbociclib is also underway.
- The DIPG-XIII cell line was treated with fixed doses of palbociclib (0.1μM, 0.5μM, 1μM, and 2.5 μM), while GSKJ4 concentrations were varied from 1.25-12.5μM at each palbociclib dose.

Conclusions & Future Directions

- Combination of the CDK4/6 inhibitor palbociclib with the HDAC inhibitor panobinostat yielded potent growth inhibition of DIPG cells.
- More generally, targeting the CDK4/6 pathway in combination with targeting the aberrant epigenome in DIPG is a promising therapeutic strategy in vitro.
- However, these data require further validation to reveal consistent synergy.
- Immunoblot analyses will be conducted to determine the mechanisms by which these pathways of CDK4/6 inhibition and epigenetic regulation lead to synergism.
- Toxicity analyses would help assess the toxicity benefit of combination therapy as suggested by this study.
- Lastly, alternate delivery methods of this combination therapy, such as through convection enhanced delivery, may help further ameliorate systemic toxicities that may still arise.

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