Combined inhibition of farnesyltransferase and MEK is effective in HRAS-mutant rhabdomyosarcoma

Patience Odentlyde1, Kai Pollard1, Ana Calizo1, Christine A. Prattis1

1Division of Pediatric Oncology, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

Background and Rationale

Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma of childhood, and RAS pathway mutations are the known driver mutations in the majority of fusion-negative (FN) RMS. Recent studies have demonstrated that HRAS mutations are enriched in infant cases of FN-RMS and can be associated with an aggressive clinical course and inferior outcomes. Using HRAS-mutant RMS cell lines and xenograft models, we have demonstrated that tipifarnib (farnesyl transferase inhibitor, FTI) decreases ERK signaling, decreases in vitro proliferation, and decreases in vivo tumor growth. The effects of tipifarnib can be incomplete, however, leading only to partial or short-lived responses. Limitations may be due to adaptive or acquired resistance, suggesting that HRAS-mutated FN-RMS may be sensitive to pathway inhibition with combination therapy that prevents or delays the emergence of adaptive resistance. Trametinib (MEK) inhibits tumor growth in xenograft models of FN-RMS but has only modest activity as a single agent, potentially due to release of negative feedback and activation of upstream signaling. The efficacy of inhibition with FTI and MEK have not been previously explored in RAS-driven FN-RMS.

Tipifarnib potentiates the effects of tipifarnib on ERK signaling

A panel of RMS cell lines (mutations as indicated) were treated with DMSO, 100 nM tipifarnib, 5 nM trametinib, or the combination for 6 or 24 hours. Phospho- and total levels of ERK and p38 pathway components, and vinculin (loading control) were determined by immunoblot from whole cell lysate (WCL).

Tipifarnib in combination with trametinib promotes myogenic differentiation

The R package EnhanceVolcano was used to generate volcano plots of the differentially expressed genes for SMS-CTR (HRAS Q61K) at 24 hrs.

Tipifarnib and trametinib more potently reduces HRAS-mutant cell proliferation

RMS Q61K and RMS Q61R cells were treated with 0, 10, 50, and 100 nM of trametinib or tipifarnib, or in combination.

Conclusions

Vertical RAS pathway inhibition with tipifarnib and trametinib inhibits 2D and 3D cell growth, ERK signaling and promotes MHC expression in HRAS mutated human RMS cell lines. These results suggest that the combination of tipifarnib and trametinib could be tested in a trial for patients with HRAS mutated RMS.

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