Long Term Effects of Transient Romidepsin Exposure on Osteosarcoma Sarcospheres

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Background:

Osteosarcoma, the most prevalent primary bone cancer, disproportionally affects adolescents and young adults. Despite aggressive chemotherapeutics, prognosis remains poor, highlighting the need for novel therapeutics. Romidepsin, a histone deacetylase inhibitor, emerged as exceptionally potent and minimally toxic in our screen of 114 FDA-approved oncology drugs using three-dimensional osteosarcoma spheroids (sarcospheres). Due to the genetic complexity of pathogenesis, differences in sensitivity exist across cell lines and patient samples. Understanding the mechanism of romidepsin is crucial for determining predictability of treatment response, especially considering its short half-life and weekly administration regimen.

Methods:

Sarcospheres derived from established cell lines (LM7, MG63.3, and 143B) or patient sample (TT2) were exposed to various concentrations of romidepsin for 24 hours. Metabolic activity was measured by resazurin reduction assays at multiple timepoints following romidepsin removal.

Results:

Effects of transient romidepsin exposure last at least 14 days. TT2 and LM7 sarcospheres do not increase in size over 48 hours of culture, and recovery is prevented at clinically achievable levels. In contrast, 143B and MG63.3 sarcospheres show growth over 48 hours and romidepsin blocks this growth. For these sarcospheres, concentrations above clinically achievable levels are required to prevent recovery.

Conclusions and Potential Impact:

Romidepsin is FDA-approved for weekly administration in lymphoma. Effects caused by transient exposure to romidepsin persisted for 14 days in slow growing patient-derived sarcospheres, suggesting weekly administration is likely sufficient for patients with osteosarcoma. Results of this study are consistent with our previous findings that there are two types of responses to romidepsin. Romidepsin causes a G2 cell cycle block and growth inhibition in 143B and MG63.3 sarcospheres, while it causes DNA damage and cell death in LM7 and TT2 sarcospheres. Further exploration of these mechanistic differences has the potential to personalize medicine by providing better predictability of response to treatment and insight into prognosis.