Cancer Res (2024) 84 (6_Supplement): 7199.
https://doi.org/10.1158/1538-7445.AM2024-7199

Abstract 7199: The retinoid X receptor (RXR) agonist IRX4204 potentiates the efficacy of trabectedin and pioglitazone in myxoid liposarcoma preclinical models

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Abstract

Myxoid liposarcoma (MLS) is characterized by a chromosomal translocation that results in the formation of the FUS-DDTI3 fusion protein, which blocks the final step of adipocytic differentiation from adipoblasts to adipocytes. Trabectedin (ET) is a marine drug able to displace FUS-DDTI3 from the promoters of its target genes, restoring adipogenesis and leading to long-lasting clinical responses in MLS patients. However, after prolonged treatments with ET, resistance occurs, and no further therapies are available. Recent studies indicate that the PPARγ agonist pioglitazone (PIO) reactivates adipocytic differentiation in MLS preclinical models resistant to ET, restoring treatment efficacy. While the combination of ET and PIO is being studied clinically, our goal here is to further potentiate the stimulation of adipocytic differentiation to obtain even better tumor growth inhibition. Since the PPARγ and the RXR heterodimerize, and the heterodimer is permissive, we will exploit this property by combining PIO with the RXR agonist IRX4204. The DL221 human MLS cell line was treated with PIO or IRX4204. To assess adipocytic differentiation, cells were stained with LD540 and DAPI for fluorescence microscopy. FABP4 and ADIPOQ expression was measured using RT-PCR. Drug efficacy and tolerability were evaluated in MLS patient-derived xenografts ML017 (sensitive) and ML017/ET (trabectedin-resistant). Mice were randomized to receive PIO (150 mg/kg p.o. qdx28), ET (0.15 mg/kg i.v. q14dx2), IRX4204 (10 mg/kg i.p. qdx28), or their combinations. PIO and IRX4204 induced mature adipocyte-like morphological alterations and lipid droplet accumulation in the DL221 cell cytoplasm, and when PIO and IRX4204 were combined, these effects were more evident. In parallel, the expression of the adipocytic markers FABP4 and ADIPOQ increased. In vivo, the addition of IRX4204 to ET and PIO improved the efficacy of treatments in both the ML017 ($p<0.0001$) and the ML017/ET ($p<0.0001$) models, causing faster tumor responses and extending animal survival. Interestingly, even in the absence of ET, the combination of PIO and IRX4204 caused a significant inhibition of tumor growth compared to the single drugs in both the ML017 ($p<0.001$) and the ML017/ET ($p<0.0001$) models. IRX4204 in combination with ET and PIO was able to improve their antitumor activity, enhancing, at least in vitro, their differentiating capabilities and inducing faster inhibition of tumor growth. The combination of IRX4204 and PIO, even without ET, could be a clinically effective option, especially for patients not suitable to receive ET or as maintenance therapy. Further studies are ongoing to better define the mechanism of action of these combinations through in vivo histological and molecular analysis.