EFFICACY OF COMBINED PI3K AND ANGIOGENESIS INHIBITION IN DEDIFFERENTIATED LIPOSARCOMA (DDLPS)

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Aim: We evaluated the efficacy of the PI3K inhibitor GDC-0941 (GDC) in combination with the angiogenesis inhibitor pazopanib (PAZ) in DDLPS xenografts with proven PI3K/AKT pathway activation.

Methods: NMRI nu/nu mice were either injected bilaterally with 5x10^6 SW872 cells or transplanted with human DDLPS (UZLX-STS3). Animals were randomized to 4 groups and treated for three weeks: vehicle, GDC (p.o., 75mg/kg/qd), PAZ (p.o., 40mg/kg/bid), GDC+PAZ (same dose/schedule as single agents). Efficacy was assessed by tumour volume, Western blotting of the signalling pathway and histological evaluation [mitosis, apoptosis, microvascular density (MVD)]. Statistics were performed using the Mann-Whitney U and Wilcoxon matched pairs tests. p<0.05 was defined as statistically significant.

Results: At the end of treatment, tumour shrinkage was observed in GDC and GDC+PAZ groups in SW872 bearing animals (38% and 52% decrease compared to baseline, p<0.05). In the patient-derived xenograft UZLX-STS3 GDC+PAZ delayed tumour growth as compared to either single agent (p<0.05). GDC as single agent caused a decrease in mitotic activity in both models (2.5 and 1.7 fold, respectively) and a 2.3 fold increase in apoptotic count in STS3 as compared to control (p<0.05). PAZ alone induced significantly lower mitotic counts in STS3 (1.8 fold), a 2.5 fold increase in apoptotic activity and significant inhibition of vascularisation as assessed by MVD (4.3 fold) compared to control group (p<0.05). In STS3 model the combination of GDC+PAZ caused an inhibition of proliferation (4.5 fold as compared to control, p<0.05), which was even more pronounced than for either single agent (p<0.05 for each), an increase in apoptosis (2.5 fold) and a decrease in vascularisation (3.3 fold) in comparison with untreated controls (p<0.05). In the both models, GDC alone suppressed the activation of the PI3K signalling pathway, which was more pronounced in GDC+PAZ treated tumours.

Conclusions: Combined inhibition of PI3K and angiogenesis results in enhanced antitumour efficacy in DDLPS mouse models which warrants further study in this highly aggressive disease.

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