

Does Metformin Increase the Effectiveness of Lenalidomide in Myeloma Treatment?

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Abstract

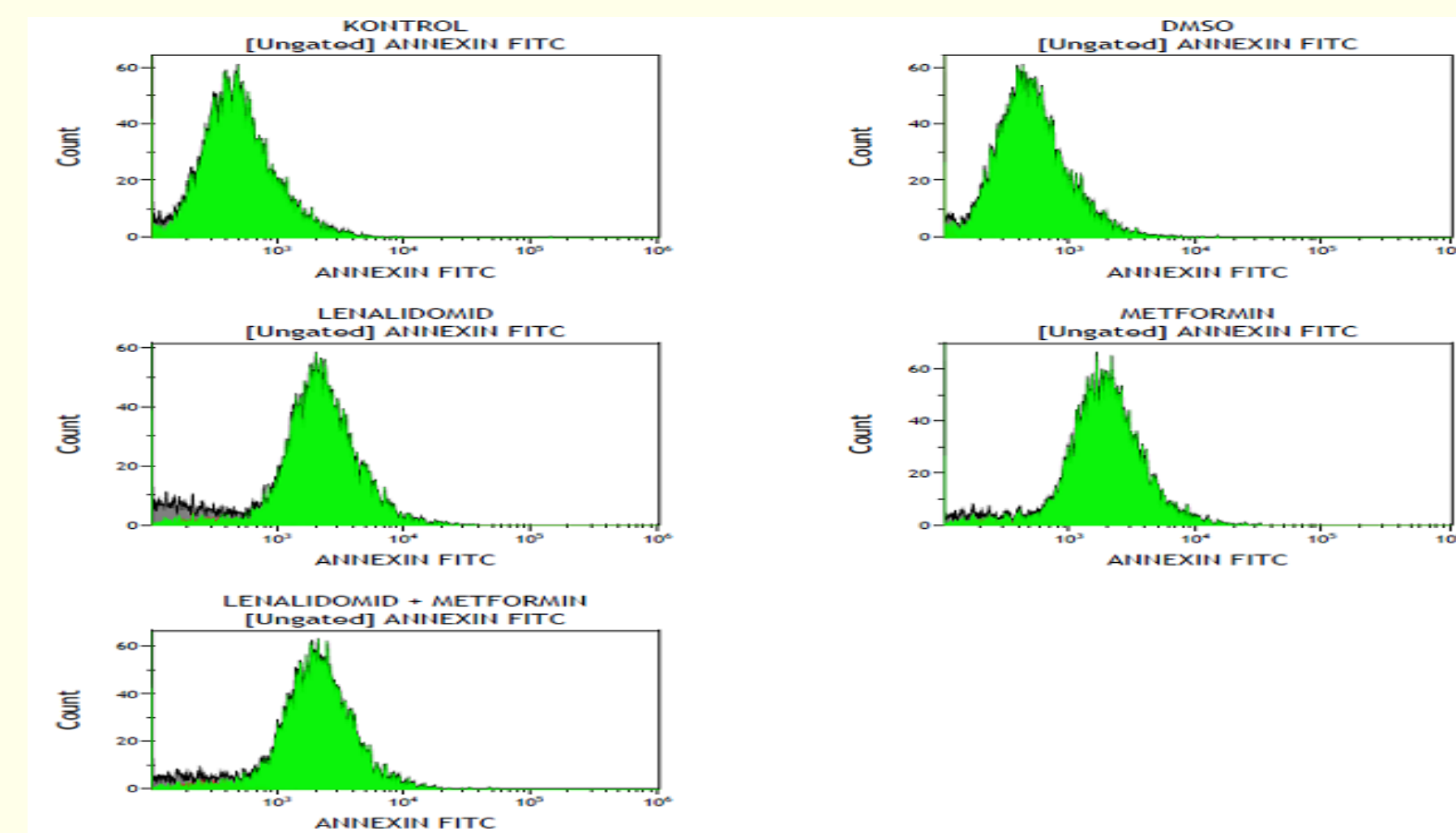
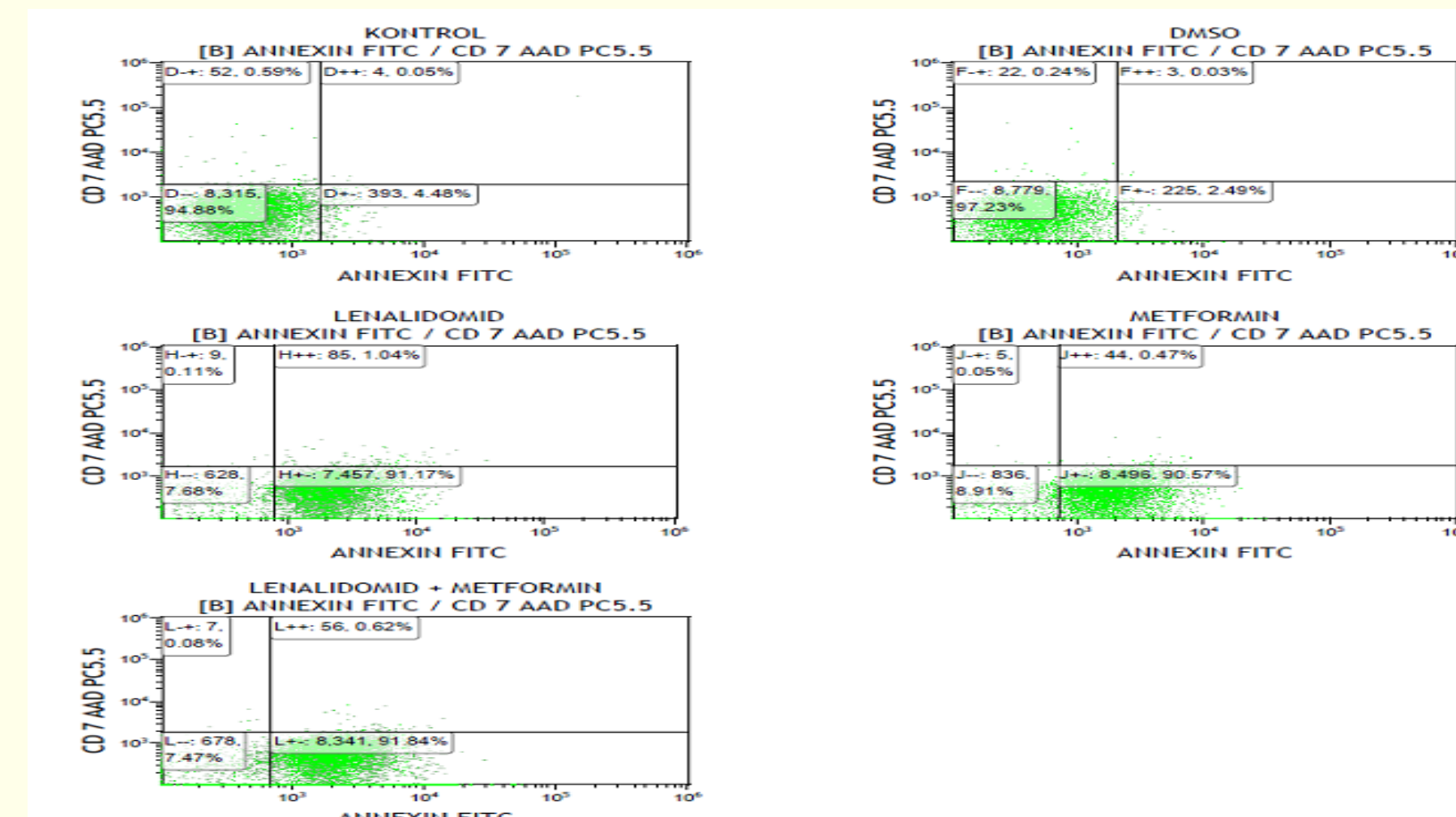
There is a need for new treatment options albeit considerable improvement in Multiple Myeloma treatment. Metformin is effective on some malign diseases such as lymphomas and myeloma. Here, we investigated the impact of metformin with or without lenalidomide on myeloma cell line using in vitro method. Metformin showed cytotoxicity and apoptosis on myeloma cells. But, there is no synergistic effect with lenalidomide. This study indicated metformin can be effective for myeloma treatment. There is a need for clinical studies for the antimyeloma effect of metformin.

Background

Metformin is an oral anti-diabetic drug, derived from biguanides. As well as it's anti-diabetic effect, it has different effects such as anti-tumor, pleiotropic, anti-angiogenesis¹. The anti-tumoral effect of metformin is classified as direct and indirect. The direct effects are AMPK-dependent and AMPK-independent. Metformin shows its indirect effect via plasma glucose and inflamatur pathways². The anti-myelom effect of metformin has been demonstrated in cell culture studies. In a study, metformin has been shown to reduce cell proliferation and to stop cell cycle at G0-G1 phases, however, it has not been shown to affect apoptosis³. In another study, it has been observed both anti-proliferative and anti-apoptotic effects in-vitro and in-vivo. Moreover, metformin has a synergistic effect with dexamethasone in this study⁴.

Objective

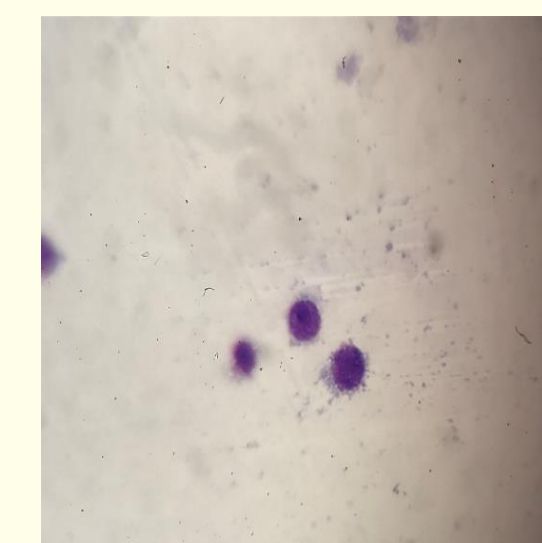
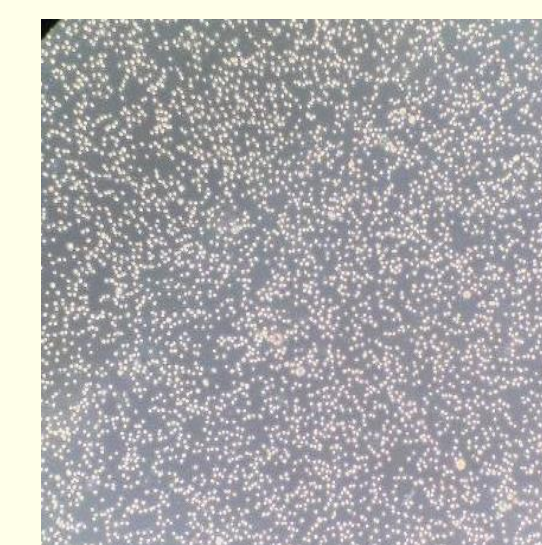
Our aim is to investigate whether oral metformin has an effect on myeloma treatment or not. Additionally, we have investigated whether metformin has a synergistic effect with lenalidomide or not.



Staining with Annexin-V FITC between groups. Groups with metformin, lenalidomide, and combination have been observed with evident staining.

Materials & Methods

The study made use of the U266 myeloma cell line. The cells were grown in RPMI 1640 medium with 10% heat-inactivated Fetal Bovine Serum, 100 U/ml penicillin, 100 mg/ml streptomycin, L-glutamine in 200 mM medium and 5% CO₂ at 37°C atmospheres and in 75 mL polystyrene flasks. The cells grown were administered various doses of metformin and lenalidomide and IC₅₀ values for both drugs were identified. Identified doses of metformin (100 mM), lenalidomide (200 µM), and a combination of these two were administered and the vitality and apoptosis were investigated using MTS/PMS and Annexin V-FITC, respectively. Results were evaluated using SPSS 21 program; the Student's t-test and one-way ANOVA were performed.



Images of cells from light microscope before (small photos) and after (large photo) metformin treatment.

Summary

The MTS/PMS experiment showed that vitality decreased in metformin, lenalidomide, and combination groups. The vitality was lower in wells that were administered metformin only and combination drugs compared to ones only administered lenalidomide, however, this difference was not statistically significant (p=0,48 and p=0,32, respectively). Significant apoptosis was identified in the metformin group compared to the control group in the flow cytometry experiment (p<0,001). No difference was found between the combined group and the lenalidomide group (p=0,39).

Discussion

The study identified a reduction in vitality and induction in apoptosis in myeloma cell lines due to metformin. On the other hand, it was revealed that in combined administration, metformin did not improve the efficacy of lenalidomide. This study is a preclinical and cell culture study. Further clinical studies with metformin would be beneficial in the treatment of Multiple Myeloma.

References

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