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IN VITRO AND IN VIVO ANTITUMOR EFFECTS OF AZIDOTHYMIDINE IN A HUMAN MULTIPLE MYELOMA CELL LINE

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Background: Azidothymidine (AZT) is an antiretroviral nucleoside analogous inhibitor of reverse transcriptase with known effects on cell proliferation, apoptosis, and angiogenesis Multiple myeloma is a severe disease and one of the steps involved in the malignant transformation of plasma cells is the activation of the nuclear factor kappa B (NF-κB) pathway.

Objective: Evaluate the in vitro cytotoxic activity of AZT in human myeloma cell lines (RPMI 8226/S and RPMI 8226/Dx5) as well as in other cell lines: human T cell lymphoblast-like, T cell leukemia, uterine sarcoma and HUVEC. The in vivo effect was also evaluated in tumor xenograft model of human multiple myeloma in nude mice.

Methods: Cells were treated with increasing concentrations of AZT (32.2 to 500μM) for 24 to 72 hours. Cytotoxicity was measured by MTT. Cell cycle and proteins Bcl-2 and p53 were evaluated by flow cytometry. For the in vivo experiments, 1x107 RPMI 8226/S cells were injected SC in the right flank of nude mice. After 7 days, animals were treated or not with AZT 12.5 μM IV every other day for 5 weeks. Thirty five genes were then investigated in the grafted tumor cells by real time polymerase chain reaction.

Results: AZT showed in vitro antitumor activity in cell lines 8226/S and 8226/Dx5 in a dose and time dependent way ($p = 0.02$), but not in the other studied cells. Histological signs of apoptosis were seen, such as cytoplasmic blebs, nuclear condensation. A significant decrease of Bcl-2 ($p < 0.001$) and p53 ($p = 0.0139$) proteins was observed in cells treated with AZT. A cell cycle arrest in S phase was also seen after 72 hours of treatment with AZT 62.5 μM. Tumor volume in nude mice treated with AZT was reduced ($p = 0.0003$). In these tumors, AZT decreased the expression of genes associated with cell proliferation (AKT1, MYC, STAT1, MAPK8, MAPK9, CCL-3, Bcl-3 and Cyclin D2), angiogenesis (VEGF, IL8), cell adhesion (ICAM1 and FN1) and NF-κB. Moreover, also in tumors, AZT induced expression of the tumor suppressor gene FOXP1, pro-apoptotic genes BID, Bcl-10 and caspase-8.

Conclusion: Azidothymidine promotes a cytotoxic effect in human multiple myeloma cells both in vitro and in vivo. This action involves the cell cycle arrest in S phase, inhibition of expression of genes that activate cell proliferation, as well as proangiogenic genes and NF-κB, and activation of apoptosis genes. Therefore, AZT could be potentially promising in the treatment of multiple myeloma.

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A KEY ROLE FOR EZH2 AND ASSOCIATED GENES IN MOUSE AND HUMAN ADULT T CELL ACUTE LEUKEMIA

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Abstract selected for oral presentation. See Speaker Abstract S8.

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ADHESION OF MULTIPLE MYELOMA CELLS TO FIBRONECTIN IS INFLUENCED BY TOLL-LIKE RECEPTOR-1 TRIGGERING

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Introduction: In multiple myeloma (MM), adhesion of malignant plasma cells to fibronectin (FN) plays an important role in pathogenesis. Although many factors, derived from MM cells or their microenvironment, have been implicated to maintain this interaction, no study has to date addressed the effect of factors derived from infection or inflammation. Furthermore, myeloma patients are vulnerable to a variety of infections, and