MultipleMyelomaHub

General MM

Ultra-high doses of vitamin C can selectively kill MM cells and lower the dose of melphalan

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In medical terms, ultra high-doses of vitamin C are referred to as 'pharmacologically-dosed ascorbic acid' (PAA). In a recent study conducted by Jiliang Xia, Hongwei Xu and Xiaoyan Zhang and colleagues from the Holden Comprehensive Cancer Center, University of Iowa, USA, and published in EBioMedicine, PAA was shown to selectively kill MM cells. Reduction in tumor burden was also observed with PAA combined with low-dose melphalan, which could lead to fewer side-effects without the loss of efficacy.

Key Highlights:

- Survival of primary $CD138^+$ cells from MM patients cultured *in-vitro* was significantly decreased following PAA treatment; the same effect was observed with cells from smoldering MM (SMM) patients but was not observed with $CD138^-$ cells from the same patients, or with cells from MGUS patients (possibly due to lower cytosolic iron)
- Different agents and combinations were tested in a xenograft mouse model: control, PAA, melphalan, carfilzomib, melphalan and PAA, carfilzomib and PAA and bortezomib
- All agents showed significant inhibition of MM cell growth ($P<0.05$), although the combination of melphalan and PAA showed a higher decrease in tumor burden and greater tumor burden reduction, compared to PAA alone or other single agents
- Treatment of xenograft mice with PAA combined with low-dose melphalan (1 mg/kg) showed significantly prolonged survival compared with low-dose melphalan alone ($p<0.05$)
- No differences in survival were observed between low and high doses of melphalan when given in combination with PAA
- The presence of iron was a pre-requisite for PAA to achieve anti-cancer activity, as high cytosolic iron catalyzes PAA auto-oxidation leading to cell death
- MM cells have a higher labile iron pool (LIP) than non-tumor cells, due to down-regulation of the iron exporter Fpn1
- The anti-cancer effect of PAA was shown to depend on LIP, since over-expression of Fpn1 led to decreased sensitivity to PAA, and iron supplementation restored sensitivity; an iron chelator lso abolished the activity of PAA
- PAA was shown to react with LIP to generate ROS, and subsequently drive mitochondria-mediated apoptosis via cleavage of apoptosis inducing factor-1 (AIF1)

Conclusion:

PAA was found to kill MM cells, particularly those with high iron levels. The mechanism by which PAA induces apoptosis was found to be mitochondria-mediated, whereby PAA reacts with LIP to generate reactive oxygen species (ROS). Synergistic effects were observed in MM treatment with melphalan in combination with PAA, with no significant

differences in efficacy between high and low doses of melphalan. This therefore suggests that administration of PAA along with melphalan could allow dose reductions of melphalan (which is toxic to non-tumor cells) without losing efficacy. It will therefore be interesting to see data from future clinical trials to test this possibility.

Abstract

High-dose chemotherapies to treat multiple myeloma (MM) can be life-threatening due to toxicities to normal cells and there is a need to target only tumor cells and/or lower standard drug dosage without losing efficacy. We show that pharmacologically-dosed ascorbic acid (PAA), in the presence of iron, leads to the formation of highly reactive oxygen species (ROS) resulting in cell death. PAA selectively kills $CD138^+$ MM tumor cells derived from MM and smoldering MM (SMM) but not from monoclonal gammopathy undetermined significance (MGUS) patients. PAA alone or in combination with melphalan inhibits tumor formation in MM xenograft mice. This study shows PAA efficacy on primary cancer cells and cell lines in vitro and in vivo.

References

1. Xia J., Xu H., Zhang X., *et al.* Multiple Myeloma Tumor Cells are Selectively Killed by Pharmacologically-dosed Ascorbic Acid. EBioMedicine. 2017 Apr;18:41-49. Epub 2017 Feb 16. DOI: 10.1016/j.ebiom.2017.02.011