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2nd International
Cancer Study & Therapy Conference
February 20-22, 2017 Baltimore, USA

Synergistic effects of oncolytic virotherapy in a bortezomib resistant syngeneic mouse model of multiple myeloma is mediated via immune modulation

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Introduction: Multiple myeloma (MM) is a plasma cell neoplasm that is considered incurable. Despite the advent of new agents the majority of MM patients relapse secondary to therapy resistance.The potential of reovirus (RV) as a novel therapeutic agent for MM under *in vitro, in vivo* and *ex vivo* conditions has been demonstrated by us and a phase I clinical trial of MM with RV therapy has shown indications of efficacy. Utilizing the syngeneic transplantable Vk*MYC bortezomib (BTZ) resistant MM mouse model, we demonstrate that mice harbouring BTZ insensitive MM tumors significantly respond to RV+BTZ combined treatment better than monotherapy. Our data indicate that this RV+BTZ synergy is manifested via, direct oncolysis in conjunction with enhanced immune activation.

Methods: C57BL/6 wt mice were divided into 2 groups and transplanted with Vk*MYC myeloma (Vk12598) and were treated as follows, (N=8): 1) vehicle control (VC), 2) live reovirus (LV), 3) dead reovirus (DV), 4) BTZ, 5) LV+BTZ, 6) DV+BTZ. Mice in group 1 were sacrificed after 4 days of treatment and their spleens and bone marrow (BM) were formalin fixed and paraffin embedded. These were assessed for CD138+ MM tumour as well as viral RNA and protein in the tumour microenvironment (TME) and a variety of immune correlates as well as apoptotic markers. Mice in group 2 were assessed for serum gamma globulins (M-spike)on a weekly basis and overall survival analysis was conducted.

Results: Mice treated with RV+BTZ demonstrated highly significant ($P<0.001$) reductions in their M-spikes at 3 and 4 weeks post treatment and superior overall survival ($P<0.001$). Analysis of tumour viral delivery/replication and immune activation in the TME as early as 4 days post treatment initiation indicated significant ($P<0.01$) viral replication, caspase 3 activity, CD3+ and NK cell accumulation in the RV+BTZ treatment.

Conclusions: Our data indicate that this RV+BTZ synergy is manifested by enhanced apoptosis, successful viral delivery via tumour associated endothelial and follicular dendritic cells and immune modulation. Since the progression of MM is associated with concomitant immune suppression and drug resistance, these results have significant implications for shaping future clinical trials.

Biography:

Dr. Chandini Thirukkumaran is a Research Associate Professor at the Tom Baker Cancer Centre, University of Calgary, Calgary, Alberta. She received her PhD in microbiology in 1994 from the University of Calgary. Following completion of a post doctoral fellowship in signal transduction at the University of Calgary she joined the Translational Research Laboratories at the Tom Baker Cancer Centre, Calgary as a Research Assistant Professor in 1999. Since then her work has focused on oncolytic viruses as treatment modality for cancer. Presently she is conducting research on multiple myeloma and breast cancer and the effects of oncolytic viruses on immune modulation when given in conjunction with “standard of care therapies” for these malignancies.