SIgN Immunology Seminar



Dr Santi Suryani

Children's Cancer Institute Australia for Medical Research

Targeting BCL-2 Pathway as a Future Therapy for Paediatric Leukaemia

Host
Dr Katja Fink
Singapore Immunology Network, A*Star

Date
Tuesday
4 August 2015

Time
11am – 12pm

Venue
SIgN Seminar Room
Immunos Building
Level 4
Biopolis

Targeting the apoptosis pathway with BH3 mimetics such as ABT-263 (navitoclax) and ABT-199 is an appealing strategy for cancer therapy. While the Bcl-2/Bcl-w/Bcl-xL inhibitor navitoclax has shown promising activity in adults with lymphoid malignancies and in preclinical models of pediatric acute lymphoblastic leukemia (ALL), its application in pediatric patients has been limited by Bcl-xL-mediated thrombocytopenia. The specific Bcl-2 inhibitor ABT-199 has shown remarkable efficacy against adult chronic lymphocytic leukemia in recent clinical trials, although its activity against pediatric ALL is yet to be tested. The aim of this study was to evaluate the *in vivo* efficacy of ABT-199 against a large panel of pediatric ALL patient-derived xenografts (PDXs), and to identify biomarkers predictive of ABT-199 response. Immune-deficient (NOD/SCID or NSG) mice inoculated with PDXs derived from patients with infant ALL harboring rearrangement of the Mixed Lineage Leukemia (MLL) oncogene, B-cell precursor ALL, BCP-ALL categorized as Ph-like, T-cell ALL or early T-cell precursor ALL were treated with ABT-199 or vehicle control. Responses were assessed by time to event measurements or stringent objective response criteria modeled after the clinical setting. ABT-199 significantly delayed the progression of 12/20 PDXs and elicited objective responses in 6/20 (30%) of PDXs (4 complete responses and 2 partial responses). No objective responses were observed in the T-ALL or ETP-ALL PDXs. By comparison, navitoclax administered on the same dose and schedule as ABT-199 elicited objective responses in ~60% of PDXs derived from the same pediatric ALL subtypes. Analysis of basal gene and protein expression revealed that high Bcl-xL and low Bcl-2 expression were significantly associated with in vivo ABT-199 resistance. Moreover, the Bcl-2/Bcl-xL gene ($P = 0.03$) and protein ($P = 0.002$) expression ratios were significantly elevated in PDXs that responded to ABT-199 in vivo compared with non-responders. Notably, Mcl-1 expression at the gene or protein level showed no significant correlation with in vivo ABT-199 sensitivity. In conclusion, the inferior objective response rate observed for ABT-199 (30%) compared with navitoclax (61%) indicates that pediatric ALL PDXs are less dependent on Bcl-2 for cell survival compared with adult chronic lymphocytic leukemia. Moreover, Bcl-xL appears to be a more significant ABT-199 resistance factor than Mcl-1 in pediatric ALL. While ABT-199 has the potential to exert significant efficacy in the treatment of aggressive and chemoresistant pediatric ALL, the prospective identification of patients who might benefit from such treatment is of paramount importance.