Novel combination therapy for treating proteasome inhibitor-resistant multiple myeloma

Byung-Gyu Kim[1,2], Sung Hee Choi[1,2], Huong Nguyen[3], Fu-Seng Liang[3], Seong-Jin Kim[4], John J. Letterio[1,2], and Alex Y. Huang[1,2]

[1]Department of Pediatrics, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106, USA
[2]Case Comprehensive Cancer Center, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106, USA
[3]Department of Chemistry, Case Western Reserve University, 11100 Euclid Avenue, Cleveland, OH 44106, USA
[4]MedPacto Inc., Seoul, Republic of Korea

Abstract

Multiple myeloma (MM) is an incurable plasma cell malignancy characterized by osteolytic bone disease and immunosuppression. Proteasome inhibitors (PIs) have remarkably improved the survival of MM patients, but dose-limiting toxicities and the development of drug resistance limit their long-term utility. Elevated TGF-β levels in MM patient sera correlate with drug resistance, disease progression, metastasis and poor prognosis. Therefore, we evaluated the anti-MM therapeutic potential of a TGF-β type I receptor kinase inhibitor, Vactosertib. *In vitro* treatment of Vactosertib synergistically inhibited the growth of bortezomib (BTZ)-resistant MM cells in combination with either BTZ or ixazomib (IXZ) by suppressing TGF-β activation of Smad2/3 and expression of *PSMB5,* which encodes the proteasome 5 catalytic subunit targeted by PIs. Oral administration of Vactosertib as a single agent decreased MM progression and mortality of the mice bearing BTZ-resistant MM. Vactosertib alone also attenuated PSMB5 expression and proteasome activity, reduced the expansion of $CD11b^{+}Gr\text{-}1^{+}$ myeloid derived suppressor cells (MDSCs) in bone marrow (BM) tumor microenvironment (TME), and diminished the population of $Foxp3^{+}$ regulatory T cells (Treg) in the spleen. Combination therapy of Vactosertib plus PI (BTZ or IXZ) exhibited a synergistic anti-myeloma effect when compared to either Vactosertib or PI alone by greatly prolonged survival and significant a reduction in both MDSCs and Tregs. Furthermore, therapy of $BCMA^{+}$ CAR T cells in combination with Vactosertib exhibited a synergistic anti-tumor effect, compared to either CAR T cells or Vactosertib. Taken together, our data provide the rationale for clinical evaluation of Vactosertib in MM and demonstrate proof-of-concept that combination of Vactosertib and either PI or cell therapy may overcome drug resistance and enhance durable patient responses.