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Bortezomib salvage therapy in refractory acute adult T-cell leukemia/lymphoma

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Outcomes for acute/leukemic adult T-cell leukemia/lymphoma (ATL) remain extremely suboptimal^{1,2}. Median survival of only nine months and five year overall survival rates of less than 30% have been recently been reported in acute ATL patients receiving best available therapy³. Treatment for refractory and relapsed disease is particularly challenging due to chemotherapy resistance^{4,5}. In *in vitro* and *in vivo* ATL models, bortezomib⁶ can induce suppression of nuclear factor- κ B (NF- κ B) activation and reduce BIRC5 expression⁷, leading to caspase-dependent apoptosis, an effect that may be augmented by concurrent chemotherapy⁸.

A 48 year old male was hospitalized with a three week history of drenching night sweats, weight loss and left upper quadrant pain. Examination and imaging demonstrated submandibular, cervical, axillary, pelvic and inguinal lymphadenopathy with massive splenomegaly. Laboratories revealed a leukocytosis of 39,000/mm³ with 66% lymphocytes, hypercalcemia at 13.6 mg/dl and LDH elevated greater than ten times the upper limit of normal. Bone marrow biopsy showed a hypercellular marrow with numerous atypical lymphoid aggregates; flow cytometry demonstrated a 51% population of abnormal CD4+, CD25+ and CD7- T lymphocytes consistent with ATL⁹. The patient tested HIV negative and HTLV-1 positive. Treatment with EPOCH chemotherapy¹⁰, oral zidovudine 300mg twice daily and intrathecal cytarabine prophylaxis was initiated. After the first cycle there

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This report describes the use of bortezomib for an indication not current approved by the US Food and Drug Administration. The patient described provided his consent in writing for this publication. The authors declare no conflicts of interest.

was RECIST progression with enlarging lymphadenopathy and increasing LDH. Bortezomib (IV) 1mg/m² on days 1, 4, 8 and 11 of each cycle was added as salvage therapy. After a single cycle of “V-EPOCH” his lymphadenopathy resolved and his LDH normalized. After four cycles of V-EPOCH peripheral blood flow cytometry and a bone marrow examination revealed no evidence of residual leukemia. After five cycles of V-EPOCH, a consolidative non-myeloablative haploidentical bone marrow transplant was undertaken but complicated by non-engraftment in the setting of CMV viremia. However, he experienced full autologous count recovery and remains in complete remission¹ 36 months since treatment completion.

This is the first report of the successful clinical use of bortezomib to treat ATL; we await with interest prospective results from the phase I/II trial (NCT01000285) “Dose-adjusted EPOCH chemotherapy with bortezomib combined with integrase inhibitor therapy for HTLV-1 Associated T-Cell Leukemia Lymphoma” currently recruiting patients at multiple centers in the United States. Itonaga and colleagues⁵ recently reported that effective immune mediated anti-leukemic salvage therapy for ATL relapse after allogeneic stem cell transplantation (SCT) was associated with chronic graft versus host disease (GVHD)¹¹. Given the diverse immunomodulatory effects associated with bortezomib, including increased susceptibility to NK cell lysis¹², altered MHC class I epitope presentation^{12,13}, enhanced early immune recovery and importantly reduction in acute and chronic GVHD following mismatched unrelated donor transplantation¹⁴, clinical trials of this class of agent in ATL relapse prevention and treatment may also be warranted, particularly in the setting of SCT.

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