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101. RED CELLS AND ERYTHROPOIESIS, STRUCTURE AND FUNCTION, METABOLISM, AND SURVIVAL, EXCLUDING IRON: POSTER II | DECEMBER 7, 2017

Short Course of Bortezomib in Anemic Patients with Refractory or Relapsed Cold Agglutinin Disease. a Phase II Prospective Study By the Gimema Group

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Background: Cold agglutinin disease (CAD) is a chronic hemolytic disorder caused by the presence of an IgM autoantibody with specificity towards red cell antigens. The autoantibody is produced by a B-cell clone, which can often be detectable with standard diagnostic work-up. Some patients with CAD require transfusions to compensate for the chronic red cell destruction. There are few therapeutic modalities of proven efficacy which include alkylating agents, rituximab alone or in combination with fludarabine or bendamustine. Bortezomib is a proteasome inhibitor which has been successfully used in Ig-producing diseases, like amyloidosis and Waldenstrom macroglobulinemia (WM). Protein metabolism is a tightly regulated process, and inhibition of its turnover using proteasome inhibitors may lead to apoptosis in protein secreting B-cell malignancies, including multiple myeloma (MM) and WM. **Aim:** We have conducted a prospective multicenter, phase II, open label study (ClinicalTrials.gov NCT01696474) to evaluate the potential efficacy of a short course of bortezomib in anemic patients with CAD requiring transfusion or with a hemoglobin concentration below 100 g/L determined at least monthly during the two months before entering the trial. **Patients and Methods:** Patients had to be refractory to at least one



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at the dose of 1,3 mg/sqm iv on days 1, 4, 8, 11. Safety evaluation, duration of transfusion independence, and the effects of treatment on the underlying clonal B-cell disorder were secondary objectives of the trial. Patients with a concomitant lymphoproliferative disorder requiring specific treatment for reasons other than CAD or with preexisting peripheral neuropathy were excluded. **Results:** Between 12-04-2012 and 03-14-2016, 21 patients have been enrolled by 6 Gimema Italian centers. Their characteristics were as follows: median age 70 years (range 53 to 85); M/F ratio: 1/2; 6 patients had concomitant or previous clonal B-cell disorder (3 CLL, 3 B-cell lymphoma) not requiring specific therapy. Previous treatments included corticosteroids, rituximab, cyclophosphamide, azathioprine or combinations of them. Median Hb concentration at study entry was 87 g/dL (range 78-102). Ten patients were transfusion-dependent. Treatment response was evaluated at three months. Two patients stopped treatment early, one at day 4 because of pulmonary embolism and the other at day 8 because of headache, respectively, and were excluded from efficacy analysis. One of them actually achieved transfusion independence in spite of treatment stop. Of 19 evaluable patients, 3 achieved complete remission, defined as normalization of hemoglobin levels and absence of symptoms or signs of hemolysis and 3 partial remission, defined as the achievement of transfusion independence or of a stable increase of > 20g/L of hemoglobin concentration in untransfused patients, for an overall response rate of 31,6%. Four of the 6 responding patients achieved transfusion independence. The small number of patients studied precluded an analysis of factors associated with response. Five grade 3 adverse events, including headache, diarrhea, increased bilirubin levels, anemia and upper respiratory tract infection (URTI) in one patient each, and one grade 4 pulmonary embolism. They were considered not related to study drug, except for URTI. Four of 6 responding patients maintained the response after 12 months from study entry (66,7%; 95% CI: 37.9-100). All patients were alive at last follow up except for one who died of septic shock during off treatment follow up, 10 months after study entry. The effects of bortezomib on underlying B-cell lymphoproliferative disorder are being evaluated. **Conclusions:** The data demonstrate that a short course of bortezomib may be effective in a subset of patients with symptomatic CAD failing previous treatments, with acceptable toxicity. Responses seem to be long-lasting in the majority of responding patients. These data provide a rationale for further investigating the potential benefits of bortezomib either by using a more prolonged treatment schedule or in combination with other active agents. The study has been supported by JANSSEN-CILAG Spa which provided bortezomib and a grant for study monitoring.

Disclosures

Rossi: *Gilead:* Membership on an entity's Board of Directors or advisory committees; *AbbVie:* Membership on an entity's Board of Directors or advisory committees; *Janssen:* Membership on an entity's Board of Directors or advisory committees; *Teva:* Membership on an entity's Board of



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advisory committees; *Amgen*: Membership on an entity's Board of Directors or advisory committees; *Sanofi*: Membership on an entity's Board of Directors or advisory committees; *Roche*: Membership on an entity's Board of Directors or advisory committees. **Zaja**: *Celgene*: Honoraria, Research Funding; *Takeda*: Honoraria; *Novartis*: Honoraria, Research Funding; *Janssen*: Honoraria; *Abbvie*: Honoraria; *Roche*: Honoraria, Research Funding; *Gilead*: Honoraria. **Mauro**: *Janssen*: Honoraria; *Abbvie*: Honoraria; *Roche*: Honoraria; *Gilead*: Honoraria. **Barcellini**: *Alexion*: Honoraria; *Agios*: Honoraria, Research Funding; *Novartis*: Honoraria.

Topics: anemia, bortezomib, cold hemagglutinin disease, transfusion, hemoglobin, upper respiratory infections, autoantibodies, b-lymphocyte disorders, follow-up, headache

Author notes

* Asterisk with author names denotes non-ASH members.

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