ORIGINAL ARTICLE

WORSE PROGNOSIS WITH HIGHER SERUM ASPARTATE AMINOTRANSFERASE AND LACTATEDEHYDROGENASE LEVELS IN MULTIPLE MYELOMA PATIENTS TREATING WITH BOTREZOMIB-DEXAMETHASONE REGIMEN: A RETROSPECTIVE STUDY

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HOW TO CITE THIS ARTICLE:
Lohit Kumar Kalita, Chayanika Kalita, Syeda Mohsina Rohman, Pabitra Kumar Gogoi, Umesh Ch. Sarma. "Worse Prognosis with Higher Serum Aspartate Aminotransferase and Lactatedehydrogenase Levels in Multiple Myeloma Patients Treating with Botrezomib-Dexamethasone Regimen: A Retrospective Study". Journal of Evidence based Medicine and Healthcare; Volume 2, Issue 26, June 29, 2015; Page: 3864-3869.

ABSTRACT: Aspartate Amino Transferase (AST) is normally present in red blood cells, liver, heart, muscle tissue, pancreas and kidneys. So, the amount of AST in the blood is directly related to the extent of the tissue damage. Lactate Dehydrogenase (LDH) is an enzyme that transfer a hydride from one molecule to another. Lactate dehydrogenase is of medical significance because it is found extensively in body tissue, such as blood cells and heart muscle. Bortezomib has recommended as novel approach to the treatment of multiple myeloma producing rapid control. **AIM:** The aim of this study was to investigate the relationship of serum Aspartate Amino Transferase (AST) and Lactate Dehydrogenase (LDH) level with prognosis of multiple myeloma treated with bortezomib-dexamethasone regimen. **MATERIAL AND METHODS:** We conducted a retrospective study of 30 newly diagnosed cases multiple myeloma treated with bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle) and dexamethasone 40 mg once in a week. **RESULTS:** We observed high levels of AST and LDH during the treatment period in maximum number of patients of multiple myeloma with ISS stage II & III. The present study suggests that the possibility that the prognosis of patients with high levels of AST and LDH might be worse. **CONCLUSION:** From the study we observed an association between worse prognosis of multiple myeloma treated with Bortezomib-dexamethasone regimen and corresponding high level of serum LDH and AST during the treatment period.
KEYWORDS: Bortezomib; Multiple myeloma; Prognosis.

INTRODUCTION: Multiple myeloma is a plasma cell neoplasm with clonal proliferation of plasma cell that accounts for approximately 10% of all hematologic malignancies.[1] A diagnosis of myeloma requires the presence of ≥10% clonal plasma cells on bone marrow examination and/or a biopsy-proven plasmacytoma, as well as evidence of end-organ damage (i.e. anemia, hypercalcaemia, renal insufficiency, or bone lesions) that is attributable to the underlying plasma cell disorder.[2] The treatment of multiple myeloma is evolving rapidly.[3] At present Besides Autologous Stem Cell Transplantation, Bortezomib-dexamethasone regimen is recommended as first line therapy in treatment of multiple myeloma. Even in the few trials that have done so, definitive overall survival or patient-reported quality-of-life differences have not been clearly demonstrated. So, there is marked heterogeneity in how newly diagnosed patients with myeloma are treated around the world.

The choice of initial therapy is often dictated by availability of drugs, age and co morbidities of the patient, and assessment of prognosis and disease aggressiveness.[3] In the present study, we retrospectively analyzed the association of serum LDH and AST with prognosis of multiple myeloma patients treated with Bortezomib – dexamethasone regimen. In addition, the current status of studies aimed at understanding these results was also reviewed.

Patients: We conducted a retrospective study of 30 patients of newly diagnosed multiple myeloma treated with bortezomib-dexamethasone regimen between November, 2010 and February, 2013. All patients who had received at least one cycle of bortezomib-dexamethasone regimen that were analyzed in this retrospective study. The diagnosis of multiple myeloma was confirmed using the International Myeloma Working Group (IMWG) criteria for diagnosis of monoclonal gammopathies.[4] The clinical stage and prognosis was determined by the International Staging System (ISS, Table-1).[5,6] The median age was 65 years old (43–87 years old), with 19 males and 11 females. Most (70.2%) had IgG or IgA myeloma.

Treatment: Thirty patients were treated with bortezomib alone (1.3mg/m2 intravenously 1, 4, 8, and 11 of every 21-day cycle) in combination with dexamethasone. All patients received 40 mg of dexamethasone on the day of each of bortezomib. In cases of hematological toxicity, the next chemotherapy schedule was delayed until there was a sufficient recovery of neutrophils or platelets. In cases of neuropathic pain or peripheral neuropathy, the dose of bortezomib would also be reduced. The median duration of follow-up was 9 months (range 6-12 months) and the median number of treatment cycles was 1 (Range 1–2 months).

RESULTS: Serum LDH & AST were measured at different stages (ISS) of disease at diagnosis, at the end of 6 months & 12 months. (Table: II, III, IV). At the end of 6 months of follow up of total 30 patients, 10(33.33%) patients was in stage-II, 14(46.67%) patients in stage-III with high LDH level comprising a total of 24(80%) with high LDH level. Similarly, at the end of 6 months of follow up, 13(43.33%) patients in stage-II, 10(33.33%) patients in stage-III with high AST level comprising a total of 23(76.67%) with high AST level. (Table – III). At the end of 12 months of follow up of 30 cases, 6(20%) patients was in stage-II, 16(53.33%) patients in stage-III with high LDH level comprising of total 22(73.33%) with high LDH level. Similarly, At the end of 12 months of follow up, 12(40%) patients in stage-II, 11(36.67%) patients in stage-III with high AST level comprising of total 23(76.67%) with high AST level.

The important prognostic factors determined by use of ISS staging system associated with overall survival were two features - AST and LDH. The prognosis of patients with high levels of AST and LDH was worse. The optimal cut-off points according to these parameters were not determined, because the investigated patient numbers in the present study i.e. the sample size were small. Therefore, further extensive studies are needed to clarify the optional cut-off points. Meanwhile, the important prognostic factors determined by International Staging System associated with progression-free survival were not detected. Hepatic dysfunction in the form of fatty liver, cholelithiasis, postcholecystectomy was observed in 4 patients (13.33%) which were serologically negative for hepatitis B and C.

DISCUSSION: Bortezomib has been approved by the Swiss Agency for Therapeutic Products for the treatment of newly diagnosed multiple myeloma in the frontline setting and in patients with newly diagnosed and relapsed/refractory multiple myeloma who have received at least one prior therapy.[7] In this study, the factors found to be significantly associated with prognosis as well as overall survival were AST and LDH levels in patients treated with bortezomib - Dexamethasone regimen. The present study also suggests the possibility that the prognosis of patients with high levels of AST and LDH might be worse than that of patients with low levels of these parameters. The blood test for AST is usually used to detect liver damage. A review of 869 cases of multiple myeloma seen at the Mayo Clinic from 1960 through 1971 revealed that initial findings was a palpable liver in 21% cases.[8] It was reported that abnormalities in liver function were characteristic, and out of 37 cases of multiple myeloma, serum level of AST was increased in 22(59.5%) cases.[9]

In our study, serum level of AST was increased in 23(76.67%) of patients at the end of 6 months of follow up and 23(76.67%) of patients at the end of 12 months of follow up. In the present study, as mentioned above, hepatic dysfunction was observed in 4 patients (13.33%). These patients were serologically negative for hepatitis B and C. So, there is a possibility that the prognosis of multiple myeloma patients with hepatic dysfunction might be worse than that of patients without this. On the other hand, it was reported that high serum LDH is associated with features of advanced disease and inferior survival in multiple myeloma.[9,10] In our study, serum level of LDH was increased in 24(80%) of patients at the end of 6 months of follow up and 22(73.33%) of patients at the end of 12 months of follow up. Therefore, we speculate that the worse prognosis of patients with high levels of AST and LDH might be associated with the advanced stages of diseases of these multiple myeloma patients. Previously, Greipp et al. reported the association between higher Durie-Salmon stage or ISS stage and worse outcome.[6] However, in the present study, our data did not reveal a significant impact for a Durie-Salmon stage or ISS stage. Also, consistent with this, several investigators reported the prognostic value of LDH in multiple myeloma patients.[11,12]

This, however, was not incorporated in any widely used staging system, although it has an ability to identify patients with an especially adverse outcome.[13,14] Because the investigated patient numbers in the present study were small, further extensive investigations are also needed to clarify this matter. According to the issue that a high AST and LDH were not associated with progression-free survival, since the late 70s, the relationship between hematological malignancies and elevated LDH has been extensively studied.[15] In conclusion, recent clinical studies, including this study, demonstrate that bortezomib has a therapeutic effect on multiple myeloma and are well tolerated in the treatment of multiple myeloma.

The strength of the present study as we have documented that there is a possibility that the prognosis of patients with high levels of AST and LDH might be worse than the prognosis of patients with low levels of AST and LDH. The weak part of the study is that, although AST and LDH had independent prognostic value for overall survival, we did not demonstrate that these were statistically significant indicators for progression-free survival. This may be a reflection of inadequate sample size. The presented study is a retrospective study, and therefore, these results should be confirmed in further prospective studies.

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Stage	Parameters
I	Serum β_2-microglobulin <3.5 mg/l and Albumin ≥3.5 g/100 ml
II	Not fitting stage I or II
III	Serum β_2-microglobulin ≥5.5 mg/l

Table 1: International Staging System of multiple myeloma

Stage	Parameters	No. of patients with high LDH level	No. of patients with high AST level
I	Serum β_2-microglobulin <3.5 mg/l and Albumin ≥3.5 g/100 ml	4	5
II	Not fitting stage I or II	17	14
III	Serum β_2-microglobulin ≥5.5 mg/l	9	11
Total		**30**	**30**

Table 2: International staging system: Number of patients with different stages of disease with high LDH & AST value: at the time of diagnosis

Stage	Parameters	No. of patients with high LDH level	No. of patients with high AST level
I	Serum β_2-microglobulin <3.5 mg/l and Albumin ≥3.5 g/100 ml	6	7
II	Not fitting stage I or II	10	13
III	Serum β_2-microglobulin ≥5.5 mg/l	14	10
Total (Stage I II & III)		**30**	**30**

Table 3: International staging system: Number of patients with different stages of disease with high LDH & AST value: at the end of 6 months of treatment

Stage	Parameters	No. of patients with high LDH level	No. of patients with high AST level
I	Serum β_2-microglobulin <3.5 mg/l and Albumin ≥3.5 g/100 ml	8	9
II	Not fitting stage I or II	6	12
III	Serum β_2-microglobulin ≥5.5 mg/l	16	11
Total		**30**	**30**

Table 4: International staging system: Number of patients with different stages of disease with high LDH & AST value: at the end of 12 months of treatment

ORIGINAL ARTICLE

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Date of Submission: 07/06/2015.
Date of Peer Review: 08/06/2015.
Date of Acceptance: 16/06/2015.
Date of Publishing: 26/06/2015.