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Early Normalization of Free Light Chains Predicts Better Outcomes in Patients with Multiple Myeloma

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ABSTRACT

Background: The half-life of free light chain is short and can be used as an early marker for tumor response in patients with multiple myeloma [MM]. This prospective study is aimed at evaluating whether early light chain response can predict response to treatment in patients with MM.

Materials and Methods: Thirty six patients with a diagnosis of MM and with an abnormal to normal light chain ratio of > 10 were included in this study.

Results: The median age at presentation was 56 years. Fourteen patients had lambda light chain disease, whereas 22 patients had kappa light chain disease. Twenty-four patients [66.6%] had reduction of abnormal to normal light chain ratio to < 10 after 2 cycles, of whom 15 [62.5%] achieved a CR or VGPR after 6 cycles. Among 12 patients who did not have reduction of abnormal to normal light chain ratio to < 10, only 1 patient achieved CR while 11 patients [91.6%] achieved a PR or less[Fishers exact p=0.004]. Median follow-up was 13 months. Median progression-free survival for the entire cohort was 15 months. One-year Progression-Free Survival was 77% vs 57.1%, [p= 0.008], respectively for patients with early normalization and those who did not show early normalization.

Conclusion: Early light chain response after 2 cycles of chemotherapy is a good predictor for treatment response in patients with MM treated with bortezomib based chemotherapy. Treatment intensification based on early light chain response merits further evaluation in a prospective trial

Keywords: Light chain response; Multiple myeloma; Prognostic marker

INTRODUCTION

Multiple myeloma results from abnormal clonal proliferation of plasma cells in the bone marrow[1]. Serum monoclonal (M) protein detection using serum protein electrophoresis is used in the diagnosis of plasma cell disorders. However, M protein may not be detected in all patients with light chain non-secretory multiple myeloma. Hence, serum free light chain (sFLC) levels have come into use in the diagnosis of MM patients since the 2000s, and an abnormal sFLC ratio is used as a surrogate marker for clonal expansion in patients with multiple myeloma.

Usually the response evaluation (for multiple myeloma) is done after 4-6 cycles of chemotherapy. Serum FLCs have short half-lives (2 to 6 hours), monitoring of sFLC level may indicate the efficacy of treatment and prognosis[2]. Several retrospective series have shown that reduction in free light chains is associated with a better prognosis in patients with multiple myeloma [2,3]. Finding early non responders with light chain response helps in identifying patients who may benefit from early treatment intensification. The present study aims to prospectively evaluate whether the normalization of free light chains after 2 cycles of chemotherapy

correlates with a better complete response rate and predicts outcome in patients with myeloma.

MATERIALS AND METHODS

This was a prospective observational study planned in the Department of Medical Oncology, Regional Cancer Centre, Thiruvananthapuram in newly diagnosed patients with Multiple myeloma with an abnormal : normal light chain ratio of >10. The inclusion criteria included newly diagnosed treatment naive cases of multiple myeloma with an altered free light chain ratio >10 who were eligible for treatment with bortezomib- based regimens with an age >18. The study was approved by institutional review board.

Primary objective of the study was to evaluate whether reduction of free light chain ratio to < 10 after 2 cycles of chemotherapy correlates with a higher chance of achieving complete response in patients with multiple myeloma. The secondary objective was to evaluate whether reduction of free light chain ratio to < 10 after 2 cycles of chemotherapy predicted a better progression free survival in patients with multiple myeloma.

All suspected patients of multiple myeloma underwent diagnostic work-up for multiple myeloma. Baseline investigations for patients included complete blood count (CBC), erythrocyte sedimentation rate, total protein, albumin, and globulin, blood urea, creatinine, urine bence jones protein, quantitative immunoglobulin assay, serum protein electrophoresis, serum protein immunofixation, urine immunofixation, serum-free light chain assay, creatinine clearance, bone marrow aspiration and biopsy, serum beta-2 microglobulin, and lactate dehydrogenase, and then results were collected. Those patients who had an altered free light chain ratio to >10 and planned to be treated with bortezomib - based regimen were considered eligible for the study. The patients received combination chemotherapy with bortezomib- based regimens for 6-8 cycles.

Patient details were prospectively followed up and free light chain response after 2 cycles of chemotherapy was documented. Complete response assessment was done after 6 cycles of chemotherapy. The patients after completing chemotherapy were planned for maintenance chemotherapy or autologous transplant depending on response. The patients were prospectively followed up till documented progression of disease or death. Toxicity to treatment was graded as per Common Terminology Criteria for Adverse Events v 4.03.

Statistics

Data were entered into Microsoft Excel and further statistical analysis was done using SPSS software. Categorical variables were summarized as frequency (%) and quantitative variables as median and range. Fisher's exact test was used to find association between light chain response and complete response rate. Kaplan-Meier method was used for survival analysis. Progression-free survival was calculated from date of diagnosis to the date of documented progression. Overall survival was calculated from date of diagnosis to the date of death due to any cause. Log-rank test was used for univariate analysis. $P < 0.05$ was taken as significant.

RESULTS

Thirty-six patients were included in the study from the period of January 2017 to July 2018. The median age at diagnosis of the entire cohort was 56 years [range 35-72]. Majority of (66.6 %) them were between 41-60 years of age. There were 22 males and 14 females in the study, giving a male: female ratio of 1.6:1. Bone pain was the most common presenting symptom seen in 31 patients [86.11%], followed by anaemic symptoms in 15 patients [41.67%] and neurological deficit in 5 patients [13.89%]. The median duration of symptoms was 2.5 months.

Five patients [14%] had an Eastern Cooperative Oncology Group [ECOG] performance status of 0, while 17[47%] patients had a performance status of 1. Eleven and three patients each had an Eastern Cooperative Oncology Group performance status of 2 and 3, respectively. Mean hemoglobin at presentation was 9.7mg/dl [range 6.8-14.6]. ESR more than 100 mm/hour at presentation was seen in 26[72.22 %] patients. Blood urea at presentation was more than 40 in 15[41.67 %] patients and serum creatinine >2 were seen in 10[27.78 %] patients.

Serum uric acid was more than 6.5 mg/dL in 18[50 %] patients.

IgG heavy chain was the most common and was seen in 24[66.67%] patients, followed by IgA disease which was seen in 4[11.11 %] patients. Eight [22.22 %] patients had light chain only disease. Kappa was the light chain seen in 22 [61.11 %] patients. Fourteen [38.89 %] patients had Lambda light chain disease. Nineteen patients had a kappa/ lambda ratio of more than 50. Median M component at presentation was 3.5 g/dl [range 0.96 to 8.12]. Median Beta 2 microglobulin at presentation was 5.8. Seven [19.44 %] patients had ISS stage I disease, while 7[19.44 %] patients had ISS stage II disease and 22[61.11 %] patients had ISS stage III disease.

All patients received bortezomib-based therapy. Bortezomib, lenalidomide plus dexona was the most common regimen and was used in 26[72.22 %] patients. Bortezomib plus Dexona was used in 5 patients [13.9%], while 3[8.33 %] patients received bortezomib, cyclophosphamide plus Dexona and 2 patients received bortezomib, thalidomide plus dexona. Thirty [83.33 %] patients received zoledronic acid along with chemotherapy from the first cycle, while 5[13.89 %] patients received zoledronic acid in later cycles as renal function improved. Sixteen [44.44 %] patients received palliative radiotherapy to bone lesions.

Most common grade II toxicity associated with treatment was sensory neuropathy seen in 21[58.33 %] patients. Grade III neuropathy was seen in 6[16.67 %] patients. Grade II fatigue was seen in 13[36.11 %] patients and grade III in 1[2.78 %] patients.

Grade II hematological toxicity was seen in 20[55.56 %] patients. Grade III hematological toxicity was seen in 4[11.11 %] patients. Grade II skin complications were seen in 8[22.22 %] patients, and there was no grade III skin toxicity. Grade II or higher gastrointestinal complications were seen in 6[16.67 %] patients, and there was no grade III gastrointestinal toxicity. Hyperglycemia requiring medications was seen in 10[27.78 %] patients. One patient developed atrial fibrillation. There were no cases of thrombosis or treatment related mortality. All 36 patients received planned 6 cycles of chemotherapy.

Treatment Response after 2 cycles of chemotherapy

The light chain response after 2 cycles of chemotherapy revealed abnormal to normal light chain ratio < 10 in 24 [66.7%] patients and abnormal to normal light chain ratio > 10 in 12[33.3%] patients [Table 1]. Of the nineteen patients who had an initial kappa/lambda ratio of more than 50, only 12[63.15%] patients showed a reduction of kappa/lambda ratio of less than 10. Whereas, 12 out of the 17[70.58%] patients who had initial kappa/lambda ratio of less than 50 were also found to have a reduction of kappa/lambda ratio of less than 10[Fishers Exact p value, 0.454].

Response after 6 cycles of chemotherapy

Complete reevaluation was done after 6 cycles of chemotherapy and showed a complete response and very good partial response in 7 and 9 patients, respectively. Nine patients had a stable disease and 3 patients had a progressive disease after 6 cycles. Fifteen [62.5%] patients out of 24 patients who had light chain response after 2 cycles had achieved a Complete Response [CR] or Very Good Partial Response [VGPR] after 6 cycles of chemotherapy. Only 1 patient achieved CR among the 12 patients who did not have reduction of abnormal to normal light chain ratio to < 10. Early light chain response correlated well with response to treatment after 6 cycles of chemotherapy [Fishers exact p=0.004]. [Table 2]

Out of the three patients who had a progressive disease after 6 cycles of chemotherapy, only one patient had early reduction of light chain response, while the other two patients did not have an early reduction of light chain ratio.

Median follow-up of the study was 13 months. Median Progression Free Survival [PFS] for the entire cohort was 15 months [Figure 1]. Six month and one year Progression-Free Survival was 88.7% and 76.9%, respectively. Median Progression-Free Survival in patients with early normalization was not reached and was 13 months for those who did not show early normalization. One-year Progression-Free Survival was 77% vs 57.1%, respectively for patients with early normalization and those without early normalization, p= 0.008 [Figure 2].

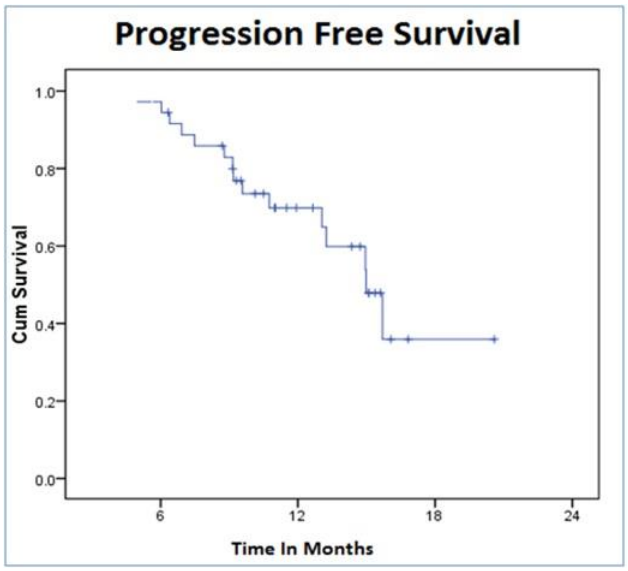

Figure 1: Progression Free Survival for entire cohort

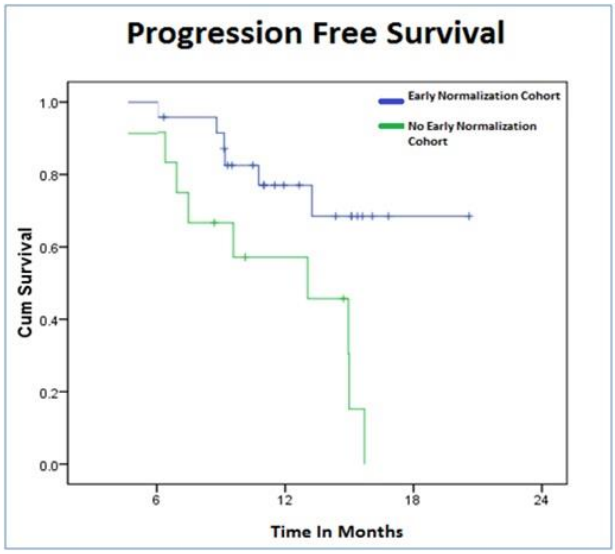

Figure 2: Progression Free Survival based on light chain normalization

Patients with an ECOG performance status of 0/1 had better one- year Progression-Free Survival 71.5% vs 67.0% for those with a PS of 2/3, but was not statistically significant. Similarly, the difference in survival outcomes with respect to the ISS stage was also not statistically significant.

The median overall survival was not reached. Six month and one year overall survival was 100% and 90.9%, respectively. Three patients had succumbed to disease as on last follow-up.

Twenty six [72.22 %] patients further went on to receive maintenance therapy. Twenty-five patients underwent bortezomib maintenance, while one patient underwent lenalidomide maintenance. Four patients further underwent 2 more cycles of same chemotherapy in view of inadequate response. Four patients underwent second-line salvage treatment. Three patients subsequently underwent autologous stem cell transplant, and 8 patients were waiting for autologous stem cell transplant.

Table 1: Treatment Response after 2 cycles of chemotherapy

Light Chain Response	Number of patients(Percentage)
Abnormal to normal light chain ratio <10	24 [66.7%]
Abnormal to normal light chain ratio > 10	12[33.3%]

Table 2: Light chain response and response rate at end of 6 cycles

	Abnormal to Normal light chain ratio < 10 after 2 Cycles	Abnormal to Normal light chain ratio > 10 after 2 Cycles
Patients with CR or VGPR after 6 cycles of chemotherapy	15[41.67 %]	1[2.78 %]
Patients with PR or less after 6 cycles of chemotherapy	9[25.00 %]	11[30.56 %]

DISCUSSION

Our study showed IgG heavy chain in 66% of the patients followed by IgA seen in about 11%. 22 % had light chain only disease. IgG and IgA constitutes majority of the heavy chain disease in multiple myeloma with light chain constituting around 15-20%[4]. IgA has more high-risk cytogenetic abnormalities and extramedullary disease and is associated with poor prognosis [5,6,7]. Light chain myeloma is associated more patients presenting with renal failure, bone disease and amyloidosis. 61% patients had kappa light chain disease, while 38% had kappa light chain disease in the present study. The lambda light chains have a significantly shorter overall survival than those secreting kappa light chains [8,9].

Light Chain response after 2 cycles revealed trend for early normalization of abnormal to normal light chain in 66.7% of the patients. This was slightly higher than published in literature with Iwama et al. reporting 40% early normalization of abnormal to normal light chain after 2 cycles of chemotherapy[3]. Gironella et al. also reported normalization of free light chain ratio in 44% of the patients who included patients treated with bortezomib thalidomide dexamethasone and melphalan-prednisone-bortezomib. But, the higher response rate in our study may be due to 72.22 % receiving bortezomib, lenalidomide plus dexamethasone [10].

The light chain normalization was 70% in patients who had a baseline kappa/lambda ratio < 50 and 63% in patients who had kappa/lambda ratio > 50 at baseline. Eighty-five percent of patients with lambda light chain disease had early normalization compared to only 54% in patients with kappa light chain disease, and these differences were statistically significant. Complete reevaluation was done after 6 cycles of chemotherapy and showed a complete response and very good partial response in 19% and 25% of the patients, respectively. Twenty-two percent of patients had a partial response. Thus, 66% of the patients had a response to chemotherapy. The response rate to bortezomib chemotherapy was lower than that in published literature [11,12]. This may be due to selection of patients with only abnormal to normal light chain ration of > 10 at diagnosis included in the present study.

Sixty-two percent of the patients who had a light chain response had achieved a Complete Response [CR] or Very Good Partial Response [VGPR] after 6 cycles of chemotherapy, while it was only 8% in patients who did not have reduction of abnormal to normal light chain ratio to < 10. The early light chain response correlated well with response to treatment after 6 cycles of chemotherapy, Fisher's exact test with p=0.004. Of the 3 patients who had progressive disease after 6 cycles of chemotherapy, one patient had early reduction of light chain response, while two patients did not have early reduction of light chain ratio. This result is comparable to the results reported by Iwama et al. who showed a normalization of free light chain in 41% patients and complete response rate of 52% in patients with normalization of free light chains and 10% in patients who did not have normalization of free light chain[3].

Median follow-up of the study was 13 months. Median Progression-Free Survival [PFS] for the entire cohort was 15 months with 6 month and 1 year Progression-Free Survival of 88.7% and 76.9%, respectively. The one- year Progression-Free Survival was better in patients with early normalization than those without early normalization (77% vs. 57.1%, p= 0.008). The median overall survival was not reached. Six months and one year overall survival was 100% and 90.9%, respectively.

Prospective nature of the study can be considered one of the merits of this study. Early light chain response was found to be a significant factor that correlates well with overall response rate and progression-free survival and can be considered as a good predictor of treatment response in patients

with MM treated with bortezomib-based chemotherapy. Early treatment intensification in patients who do not show early light chain response is a potential treatment strategy to improve outcomes in these patents. Treatment intensification based on early light chain response merits evaluation in a prospective trial to assess its usefulness.

The lack of cytogenetic evaluation and use of conventional ISS staging system remain one of the demerits of the study. But, this study represents most of the developing world where still cytogenetic studies and implementation and R-ISS staging are still far from being followed. The small sample size may be another demerit of this study.

CONCLUSION

Early light chain response was seen in 66% of the patients. Patients with early light chain response after 2 cycles of chemotherapy had a statistically significant correlation to the response to treatment after 6 cycles of chemotherapy. Patients with early light chain response after 2 cycles of chemotherapy also had a better one-year overall survival of 77% vs 57.1%. Early light chain response is a good predictor of treatment response in patients with MM treated with bortezomib-based chemotherapy. Treatment intensification based on early light chain response merits further evaluation in a prospective trial.

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