Curr Cancer Rep, 2021, 3(1): 110-118
DOI: 10.25082/CCR.2021.01.006

RESEARCH ARTICLE

Day 21 serum Free Light Chain (FLC) levels as a predictor of response to therapy in symptomatic multiple myeloma

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Received: June 10, 2021;
Accepted: August 26, 2021;
Published: September 9, 2021

Citation: Langer S, Mulam LM, Gupta N, *et al*. Day 21 serum Free Light Chain (FLC) levels as a predictor of response to therapy in symptomatic multiple myeloma. *Curr Cancer Rep*, 2021, **3**(1): 110-118. https://doi.org/10.25082/CCR.2021.01.006

Abstract: **Objective**: To study the predictive value of reduction of involved free light chain level on Day 21 of chemotherapy for achievement of VGPR after 4 cycles of induction chemotherapy. **Methods**: We conducted a prospective observational study in twenty-eight patients of newly diagnosed Multiple Myeloma with iFLC $\geq$ 100 mg/L. Serum FLC assay was done at baseline and on day 21 of therapy. All patients were followed up till the end of induction therapy for response assessment based on the IMWG criteria. Receiver Operator Characteristic (ROC) curve analysis was done to determine the cut off value of per cent reduction in day 21 iFLC for achievement of VGPR or better. **Results:** After the induction chemotherapy, out of 28 patients, 13 patients achieved CR, 8 patients achieved VGPR, 4 patients achieved PR and 2 patients had stable disease ($\geq$ VGPR = 21 patients, $<$ VGPR = 6 patients). One patient expired after 2nd cycle of chemotherapy. The mean per cent reduction in day 21 iFLC level as compared to baseline was 91.5% and 57.1% in patients achieving $\geq$ VGPR and $\geq$ VGPR ($P < 0.0001$), respectively. No other baseline parameter was found to be significantly different between the 2 groups. ROC curve analysis demonstrated a cut off of 84% reduction in iFLC value on day 21 (AUC of 0.937) had a sensitivity of 85.7% and a specificity of 100% in predicting the achievement of VGPR after four cycles of induction chemotherapy. **Conclusion:** Monitoring iFLC levels on Day 21 can be used as an important tool for early identification of responders/non-responders to myeloma therapy. Day 21 serum FLC assay may have a potential role in the real-time assessment of treatment response in newly diagnosed myeloma patients.

Keywords: multiple myeloma, prognosis, serum Free Light Chain assay

1 Introduction

The incidence of Multiple myeloma is increasing with time, in view of the newer investigation modalities and the updated diagnostic criteria. Multiple myeloma is considered to be most treatment sensitive at diagnosis. Overall survival in multiple myeloma has definitely improved in the last 15 years, largely due to the emergence of newer treatment modalities [1]. Almost all patients do relapse post induction and consolidation therapy, hence, markers which detect the relapse of disease are essential during follow up. Tools for detecting the efficacy of therapy are equally important in monitoring the disease response. Though baseline prognostic characters like cytogenetics, ISS scoring and staging to some extent determine the prognosis in plasma cell myeloma, the dynamic parameters like free light chain levels and minimal residual disease are now increasingly used to determine response to treatment and alter therapy if required. With treatment induced reduction in malignant plasma cells, the serum Free Light Chain (sFLC) concentrations tend to decrease rapidly and precipitously. Thus measurement of sFLC levels at short time intervals has been an important guide to the response to treatment, early detection of treatment failure or disease relapse.

There are many studies which have evaluated the importance of involved FLC in the monitoring of patients of multiple myeloma on therapy and early sFLC response indicating efficacy of therapy. The short half-life on free light chains (2-6 hours) as compared to that of M protein (12 days) makes it an important real time marker in determining the early response to therapy in myeloma patients [2]. Attempts have been made to study reduction in involved free light chain post chemotherapy, to monitor response and correlate with the achievement of very good partial response (VGPR) [3]. Studies have shown that normalization of the sFLC ratio and significant reductions in iFLC after initial treatment indicating better response rates. One study conducted by Hansen *et al.* [4] measured the serial levels of M protein and serum free light chain after starting therapy in myeloma patients and concluded that 80% reduction in iFLC at day 21 could

predict the achievement of VGPR post 4 cycles of induction chemotherapy with a sensitivity of 87.5% and a specificity of 100%. In contrast they found that a fall in M-protein could be appreciated only after 130 days of starting treatment. However, Indian data regarding serum free light chain assay as a predictor of response to therapy is lacking. The present study was conducted with an aim to determine the prognostic significance of serum free light chain assay in the assessment of response to therapy in myeloma patients.

2 Aim of the study

To study the predictive value of reduction of involved serum free light chain levels on Day 21 of chemotherapy, from baseline, for achievement of very good partial response (VGPR) after 4 monthly cycles of induction chemotherapy.

3 Materials and methods

This prospective observational study was carried out in the Department of Hematology, Sir Ganga Ram Hospital, over a period of one and a half year. The study was started after obtaining approval from ethics committee. As per the study done by Hansen *et al.* [4], the specificity of fall of iFLC at day 21 to predict achievement of VGPR was 100%. Thus, we have used specificity of 99% for calculating sample size using the two-step formula and minimum of 21 patients were required for our study as per calculation.

3.1 Inclusion & exclusion criteria

Newly diagnosed cases of Multiple Myeloma (based on diagnostic criteria in IMWG guidelines 2014) being started on induction chemotherapy as per standard of care with involved serum FLC $\geq$ 100 mg/L were included in the study. Patients with multiple myeloma with dialysis dependent kidney disease or pre-existing chronic kidney disease (CKD) were excluded from the study. Before enrolling the patient in study the informed consent was obtained. They were explained about the study and also given a detailed patient information sheet. The consent forms were signed after satisfying all queries. A comprehensive clinical history was recorded and complete physical examination was done.

3.2 Investigations

The following investigations were carried out on the patients at baseline(done as per standard of care for Multiple Myeloma): Complete Blood Count (CBC), Differential Leucocyte Count (DLC), Peripheral Smear (PS), Erythrocyte Sedimentation Rate (ESR), Liver function tests (LFT), Kidney function tests (KFT), Bone marrow Aspiration & Biopsy, Lactate dehydrogenase (LDH), along with Serum Protein Electrophoresis (SPEP) and Immunofixation (SIFE), Serum Free Light Chain assay (sFLC), β2 microglobulin, Immunoglobulin levels (the latter 5 investigations collectively done as Comprehensive Myeloma Panel at our institute). FISH analysis for Myeloma was done wherever feasible. Imaging studies including Skeletal survey by X-ray, Magnetic resonance imaging (MRI) or Computerised tomography (CT) scans or whole body Positron emission tomography CT scan (PET-CT) was done as per requirement. One peripheral blood sample on day 21 of chemotherapy was taken for our study to assess the serum free light chain levels and ratio. At the end of induction chemotherapy (4 monthly cycles of triple drug regimen) response to therapy was assessed by repeating the baseline investigations including the comprehensive myeloma panel.

3.3 Technique: Serum free light chain assay

The Freelite Serum free light chain assay was performed using the SPAPLUS analyser by The Binding Site using polyclonal reagents to measure the free light chains [5]. It is an turbidimetric assay composed of two sensitive and specific immunodiagnostic tests to measure kappa (κ) and lambda (λ) free light chains levels. It is based on the principle of turbidimetry, the concentration of a soluble antigen is determined by the addition of the appropriate antibody in a reaction vessel or cuvette. A beam of light, wavelength measuring 600 nm, is passed through the cuvette and, as the antigen-antibody reaction proceeds, light scatter is monitored by measuring the decrease in intensity of the incident beam of light. A series of calibrators of known antigen concentration

are assayed initially to produce a calibration curve of measured light scatter versus antigen concentration and the results are read by the analyser from the calibration curve.

3.4 Treatment

The patients were treated as per protocol [1]. Most patients received Bortezomib-based triple drug regimens. Patients with renal failure were given thalidomide instead of lenalidomide in view of renal safety of thalidomide. One patient received Lenalidomide and Dexamethasone (Two drug regimen) in view of her age and pre-existing comorbidities. All patients received 4-monthly cycles of induction chemotherapy and were assessed for the response of the initial therapy. Eligible patients were taken up for Autologous stem cell transplantation followed by maintenance chemotherapy. Transplant ineligible patients were given maintenance chemotherapy and followed up.

3.5 Follow up

Newly diagnosed cases of multiple myeloma started on induction chemotherapy were followed up until the end of 4 cycles of chemotherapy and assessed for the response to therapy. At the end of 4 monthly cycles of chemotherapy, patients were assessed for the response, based on the serum M-protein level and serum Free Light Chain level, and were divided into 2 groups based on the achievement or not achievement of VGPR (Very Good Partial Response) *i.e* $\geq$ VGPR ($>$ 90% reduction in serum M-protein and if the serum and urine M-protein are unmeasurable, then $>$ 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels) or $<$ VGPR ($<$ 90% reduction in serum M-protein or $<$ 90% decrease in the difference between involved and uninvolved free light chain (FLC) levels).

3.6 Statistical analysis

Data base was created on MS Excel and SPSS software was used for descriptive and inferential analysis. Linear regression analysis was done to assess the correlation between baseline parameters. Comparison between the baseline parameters between the two groups ($\geq$ VGPR and $<$ VGPR) was done using unpaired T-tests. Predictive value of fall in involved free light chain on day 21 was assessed by preparing ROC curves and best cut offs were generated.

4 Results and analysis

A total of 44 patients diagnosed as Multiple Myeloma on the basis of clinical and laboratory parameters as per the new IMWG diagnostic criteria of 2014, along with iFLC $>$ 100 mg/L were enrolled in the study. Out of the 44 patients, 2 patients died within few days of diagnosis, 6 patients were lost to follow up, 2 patients refused to receive chemotherapy and Day 21 blood sample for Free light chain assay could not be obtained in 6 patients. Day 21 sample for free light chain assay was obtained in 28 patients, and all these patients were followed up till the end of induction chemotherapy to assess the response to treatment. One patient died after 2nd cycle of chemotherapy hence, excluded from the analysis. So, the analysis could be done in 27 patients. Baseline investigations were carried out in all 28 patients.

The study flowchart is depicted in Figure 1.

4.1 Results

In our study, 28 patients of MM, with involved FLC $\geq$ 100 mg/L were included and were followed up till the end of chemotherapy to assess for response to treatment. One patient had died after 2nd cycle of chemotherapy hence statistical analysis was done in 27 patients. Along with baseline parameters, serum FLC assay was done on Day 21 of initiation of chemotherapy. After induction chemotherapy, the response assessment as done based on the IMWG criteria.

4.2 Clinical parameters

The median age at diagnosis was 60.3 years and the patients age ranged from 31-81 years, with maximum patients in the 6th and 7th decade with a male: female ratio was 1.33:1(16 males and 14 females). The most common presenting feature in our study was fatigue in 89.2% patients followed by bone pains in 53.5% patients. Hypercalcemia was present in 28.5%, 60.7%

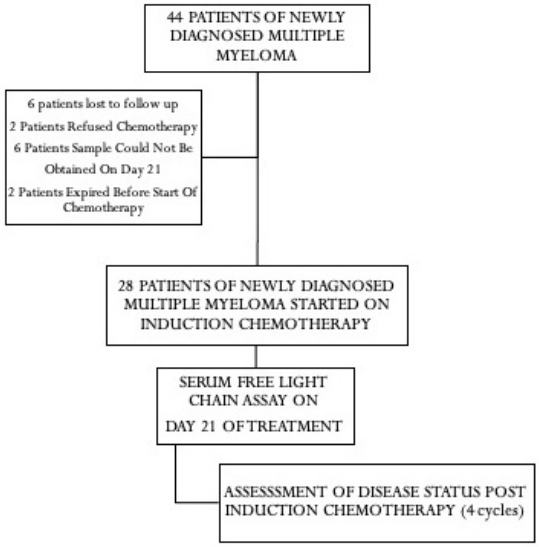

Figure 1 Study flowchart

presented with renal failure, anemia was present in 85.7%, and lytic bone lesions in 71.5% patients. We had an increased proportion of patients with renal failure.

4.3 Laboratory parameters

Patient characteristics and the median laboratory values are illustrated in Table 1.

Table 1 General characteristics of the study population (N = 28)

Variable	Value
Age	**Mean(Range)**
	60.3 (31-81)
Sex	**N(%)**
Male	16 (57%)
Female	12 (43%)
M-protein	**N(%)**
IgG	12 (43%)
IgA	8 (28%)
Light chain only	4 (14%)
Involved free light chain	**N(%)**
Kappa	15 (54%)
Lambda	13 (46%)
Treatment regimen	**N(%)**
BRD	14 (50%)
BTD	12 (43%)
RD	1 (3.5%)
CyBorD	1 (3.5%)
Pretreatment variables	**Median(Range)**
M protein (g/L)	3.27 (0.53-5.99)
iFlc (mg/L)	1948 (101.8-36766)
FLC ratio	87.38 (6.16-593.2)
Laboratory parameters	**Median(Range)**
Hb (g/dL)	7.8 (5.2-13.2)
Creatinine (mg/dL)	1.98 (0.46-15.98)
e-GFR (ml/min)	31.4(2.5-112.8)
Calcium (mg/dL)	9.75 (8.4-16)
ESR (mm 1st hr)	89 (2-160)
ISS	**N(%)**
I	1 (4.5%)
II	4 (18%)
III	17 (77.5%)

Amongst the baseline parameters, we found significant correlation between the serum creatinine and involved free light chain levels and ratio which indicate that renal involvement is associated with increased iFLC levels and FLC ratio, as the free light chain excretion is impaired in renal failure. There was also significant correlation between the β 2-microglobulin and involved FLC and involved/uninvolved FLC ratio, *i.e.* in patients with higher levels of the β 2-microglobulin, the iFLC and ratio were higher. However, we did not find any significant correlation between other baseline parameters.

4.4 Serum FLC assay on Day 21

We found that involved FLC value on Day 21 was decreased in all patients with a mean reduction of 84.34% (Range: 29.83-99.82%) and there was $\geq$ 80% decrease in iFLC in 21 patients and 7 patients had $<$ 80% decrease in iFLC.

4.5 Assessment of response to therapy

We assessed the response to treatment after 4 cycles of initial chemotherapy as per IMWG response criteria and out of 27 patients, 13 patients had achieved CR, 8 patients achieved VGPR, 4 patients had PR and 2 patients had Stable disease. 21 out of 27 patients (77.8%) had achieved $\geq$ VGPR and 6 patients (22.2%) had achieved $<$ VGPR.

We found a significant difference in percentage decrease in involved free light chain on Day 21 in patients who achieved $\geq$ VGPR (91.5% $\pm$ 12.4) and those patients who did not achieve VGPR (57.1% $\pm$ 21.3) with a P value of $<$0.0001. (Figure 2)

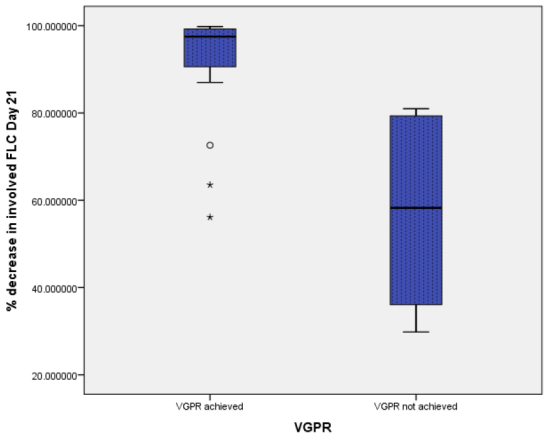

Figure 2 Boxplots for % decrease in involved FLC on day 21 between VGPR achieved and not achieved

In patients who achieved $\geq$ VGPR, the mean percentage reduction in iFLC on day 21 was 91.5% which was comparable to the study by Hansen *et al.* in which the mean percentage reduction in iFLC on day 21 was 92.3%. We found no significant difference between the hematological and biochemical parameters in patients who achieved $\geq$ VGPR and $<$ VGPR.

4.6 Correlation between reduction of iFLC on Day 21 and achievement of $\geq$ VGPR

The main objective of our study was to assess the sensitivity and specificity of % reduction in involved free light chain level on Day 21 to assess the achievement of $\geq$ VGPR. We analysed the % reduction in involved free light chain level on Day 21 in patients who achieved $\geq$ VGPR and $<$ VGPR and ROC curves were generated (Figure 3) and a reduction of 83.99% (84%) was found to be the best cut off to predict the achievement of VGPR with a sensitivity of 85.7% and a specificity of 100% with AUC (area under the curve Table 2) of 0.93.

Table 2 Area under the curve (Variable(s): DECPERINVFLC21)

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
0.937	0.046	0.001	0.846	1.000

Notes: a. Under the nonparametric assumption; b. Null hypothesis: true area = 0.5

There was no correlation between baseline parameters and percentage reduction in FLC on day 21 using linear regression analysis.

We analyzed the sensitivity and specificity of reduction in iFLC on Day 21 in predicting renal recovery. We had 13 patients with serum creatinine of $\geq$ 2 mg/dL who were assessed for renal recovery. We found that 84% reduction in iFLC value was associated with renal recovery with a sensitivity and specificity of 77.7% and 75% respectively.

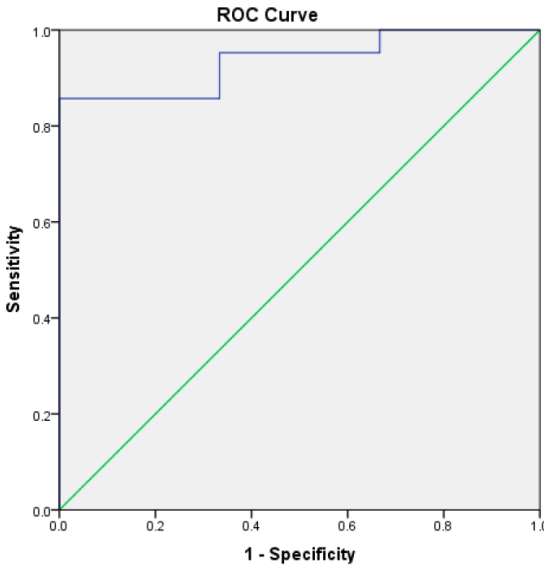

Figure 3 ROC analysis

5 Discussion

As with other haematological malignancies, in Multiple Myeloma there are a plethora of markers at diagnosis including adverse cytogenetics which predict survival [1]. However the true measure of the patient's survival and prognosis is the response of the disease to the available treatment. A patient with good risk baseline features at times do not respond well to treatment whereas the patients with predicted poor outcome achieve remission with aggressive chemotherapy. Therefore more and more the functional and real time parameters of disease are being used to predict the course of disease.

Serum Free Light Chains have shorter half-life and with the development of robust assays, involved free light chains in patients of multiple myeloma can be measured rapidly and can predict much earlier the response to chemotherapy [2]. Studies have shown that the patients who achieved VGPR have better event free and progression free survival. The rapid and greater percentage reduction in involved serum free light chain has been found to be associated with attainment of VGPR and hence can help in predicting the prognosis and course of disease.

A number of studies have looked into the prognostic effect of involved free light chain (iFLC) and the serum free light chain ratio at baseline as a marker of survival [6, 7]. In addition, a few studies have assessed the early reduction of free light chain levels to predict the response to therapy as compared to the reduction in M protein levels.

Mead *et al.* [8] in their study in 17 patients of MM had noted that the extent of change in the FLC concentrations was seen to be greater than that of the total intact immunoglobulin in all patients, the range of FLC reduction being 2.11678-fold (mean 219-fold) as compared to the range of total, intact immunoglobulin reduction was 1.588-fold (mean 14.6-fold). Dejoie *et al.* [9] in 2016 have evaluated 113 patients of MM and found that elevated iFLC or an abnormal κ / λ sFLC ratio after 3 treatment cycles associated with poorer PFS ($p = 0.006$ and $p < 0.0001$, respectively) along with poor overall survival($P = 0.022$).

However, there are a few studies with contrasting outcomes. Dispenzieri *et al.* [10] in 2008 analyzed the value of serum free light chain levels in 399 patients of multiple myeloma and had assessed the reduction of both serum FLC and M protein levels two months following induction therapy and not find serum FLC monitoring to have an added advantage over measurement of M protein. They have also concluded that baseline FLC could not predict the survival (OS and PFS) in contrast to other studies. Mori *et al.* [11] studied 73 newly diagnosed multiple myeloma patients receiving induction therapy and have stated that addition of FLC to M-protein further informs the characterization of residual disease status post-induction therapy as a biomarker, but M protein according to them was a better indicator of disease response. Van Rhee *et al.* [12] in their study, measured the SFLC levels at baseline, within 7 days of first cycle, before second induction cycle and before first transplantation, and have concluded that high baseline levels of FLC ($\geq$ 750 mg/L) along with steeper reduction after therapy indicated more aggressive disease and was associated with inferior survival. This higher reduction indicating inferior survival is in

contrast to the other studies which mention that more reduction in involved FLC indicates better survival.

Hansen *et al.* [4], in their study in 36 patients with symptomatic multiple myeloma, had measured values of iFLC and M-protein at the baseline, every day for 5 week days from the start of treatment, and after 2, 3 and 6 weeks. Ten patients with iFLC >75 mg/L achieved a reduction of 80% or more at day 21 after start of treatment and nine of these obtained ≥ VGPR. They had found that 80% reduction in iFLC at day 21 could predict the achievement of VGPR post 4 cycles of chemotherapy with a sensitivity of 87.5% and a specificity of 100%, where as a fall in M protein could be appreciated only after 130 days of starting treatment. hence Day 21 can be used as a reasonable time point to assess changes in iFLC to predict the goal of achieving at least VGPR post chemotherapy.

In our study, 28 patients of MM, we found a significant difference in percentage decrease in involved free light chain on Day 21 in patients who achieved ≥ VGPR (91.5% ± 12.4) and those patients who did not achieve VGPR(57.1% ± 21.3) with a P value of < 0.0001. In patients who achieved ≥ VGPR, the mean reduction in iFLC on day 21 was 91.5% which was comparable to the study by Hansen *et al.* in which the mean reduction in iFLC on day 21 was 92.3%. We found no significant difference between the hematological and biochemical parameters in patients who achieved ≥ VGPR and < VGPR. The baseline levels of iFLC were very diverse among our patients ranging from 101.8-36,776 mg/L, thus the per cent reductions in very high baseline values have the possibility of declining faster and steeper than lower values as has been discussed by Dispenzieri *et al.* [10].

The main objective of our study was to assess the sensitivity and specificity of per cent reduction in involved free light chain level on Day 21 to assess the achievement of ≥ VGPR. We analysed the percentage reduction in involved free light chain level on Day 21 in patients who achieved ≥ VGPR and < VGPR and ROC curves were generated and a reduction of 83.99% (84%) was found to be the best cut off to predict the achievement of VGPR with a sensitivity of 85.7% and a specificity of 100%, and AUC of 0.937. Hansen *et al.* [4] have found a cut off of 80% reduction in iFLC at day 21 as a predictor of VGPR to provide a sensitivity of 87.5% and a specificity of 100%. The mild difference in the cut off in both the studies (84% *vs* 80%) could be due to the higher disease burden in our population requiring higher reduction of FLC on day 21 to predict the achievement of VGPR. Hansen *et al.* [4] had also measured the M protein levels on Day 21 and had not found significant reduction in M protein levels in view of the long half-life of M protein and a decrease of > 90% could be obtained after 130 days of start of therapy. Hence measurement of M-protein levels on Day 21 was not done in our study. (see Table 3)

Table 3 Comparison of our study with the study by Hansen *et al.* [4]

Study	% reduction in iFLC to predict achievement of VGPR	Sensitivity (%)	Specificity (%)
Our study	84	85.7	100
Hansen *et al.* [3]	80	87.5	100

There are a few studies showing early decrease in involved free light chain was associated with improved renal outcome in MM patients. Hutchison *et al.* [13] in their study on 39 patients with biopsy proven myeloma kidney, had found a linear relationship between FLC reduction and renal recovery, with a 60% reduction in FLC by day 21 being associated with renal recovery for 80% of the population. A retrospective analysis of 279 patients by Sugihara *et al.* [14] have found that reduction of iFLC 95% at day 21 (P = 0.015) and urinary albumin ≦ 25% (P = 0.007) was significant for any renal response in patients with myeloma kidney. In our study, we found that 84% reduction in iFLC value was associated with renal recovery with a sensitivity and specificity of 77.7% and 75% respectively. Early reduction of iFLC in predicting renal recovery was established in the above studies, however, due to small sample size in our study, we could not establish a definite correlation between early decrease in iFLC and renal recovery. A study on a larger number of Indian patients with renal involvement may be required to shed light in the aspect.

We also analysed the correlation between baseline parameters and percentage reduction in FLC on day 21 using linear regression but we did not find any significant correlation between the two. There was also significant correlation between the β2-microglobulin and involved FLC and involved/uninvolved FLC ratio at baseline, *i.e.* in patients with higher levels of the β2-microglobulin, the iFLC and ratio were higher, indicating higher burden of disease as β2-microglobulin is an established independent prognostic marker in MM.

In our study, though the number of patients were less due to limitations of time, we could clearly demonstrate the importance of adding serum free light chain assay on day 21 of induction

chemotherapy as a surrogate marker of response to therapy by measuring the per cent reduction of iFLC as compared to baseline.

There are a few limitations in our study. Firstly, the number of patients in the group that did not achieve VGPR (6 patients) is very less compared to the patients who have achieved VGPR or more (21 patients). Secondly, all the patients could not be followed up to assess the overall survival (OS) and progression free survival (PFS) as the duration of our study was limited. However, we do plan to extend the study further. So, Serum free light chain assay being a simple and effective test to assess the burden of disease, evaluation of Day 21 serum free light chain assay could have a potential role as an early predictor of response to therapy.

6 Conclusion

Serum Free Light Chain assay on Day 21 of starting treatment can be done as a surrogate marker to predict the response to therapy in Multiple Myeloma early in the course of the treatment and $> 84\%$ reduction of iFLC is strongly associated with achievement of VGPR or better. This parameter could also be utilized in intensification or change of therapy if required. However, it is needed to investigate further to assess the reduction of iFLC on Day 21 for prediction of overall response.

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(Edited by Snowy Wang)