Serum Free Light Chain Assessment Early After Stem Cell Transplantation as a Prognostic Factor in Multiple Myeloma

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Abstract

A retrospective study of patients with multiple myeloma undergoing autologous stem cell transplantation (SCT) found that serial monitoring of serum free light chains early after SCT is able to identify patients at high risk of early relapse.

Background: Multiple myeloma is an incurable cancer commonly treated with stem cell transplantation (SCT). Response is traditionally evaluated 100 days after SCT, both to allow for hematopoietic reconstitution and due to immunoglobulins' long half-lives. Free light chains (FLC) have significantly shorter half-lives and may provide evidence of response or treatment failure earlier after SCT. **Patients and Methods:** We retrospectively studied 83 consecutive patients with multiple myeloma who underwent SCT and found 69 who had FLC measured 30 or 60 days after SCT. Using conventional FLC response criteria, we considered a patient to be at high risk for early relapse if he or she failed to experience a partial response by day 30 or 60. **Results:** After a median overall follow-up of only 335 days, these high-risk patients had significantly shorter progression-free survival (median, 98 vs. 335 days, $P = .001$) and overall survival (366 days vs. median not reached, $P = .016$). **Conclusion:** Early FLC assessment either 1 or 2 months after SCT using standard FLC response criteria was able to identify a subset of patients at high risk of early relapse, and these patients may benefit from earlier interventions.

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Introduction

Multiple myeloma (MM) was the first cancer identified to have a measurable biomarker, first described in 1848.[1] The serum M-spike has been used has been used for over 90 years for the diagnosis, treatment response, and prognosis of MM, and in 2001 a highly sensitive assay to measure free light chains (FLC) became commercially available.[2-5] Serum FLC are useful in the diagnosis, risk stratification, and treatment response assessment of plasma cell disorders.[6-16]

High-dose chemotherapy with autologous stem cell rescue (stem cell transplantation, SCT) remains an important component of treatment consolidation after induction and as a salvage therapy.[17,18] Traditionally, restaging has been performed 100 days after SCT, not only to allow for hematopoietic reconstitution but also in part due to the 6- to 25-day half-life of intact immunoglobulins; however, FLC have much shorter half-lives of approximately 6 hours. Pratt et al[19] measured FLC daily after SCT in 19 patients to characterize the kinetics of FLC early after SCT. Patients had rapid reductions in FLC with a median half-life of 4 days to very low levels (median, < 5 mg/L). FLC recovered to the normal range at a median of 17 days after SCT, but recovery occurred with both involved and uninvolved FLC with a normal ratio. These data suggest that early assessment of FLC after SCT may be able to identify a subgroup of patients whose disease fails to respond to SCT and who are at high risk of early relapse.

The role of FLC in monitoring treatment response early after SCT is not currently known; however, since the advent of novel agents, more patients are entering SCT having experienced a very good partial response (PR) or better, and no longer even have a measurable M-spike to assess their response.[20] Two retrospective studies have examined the prognostic value of FLC in SCT. Giarin et al included 203 newly diagnosed patients who underwent

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induction with vincristine, doxorubicin, and dexamethasone (VAD) and had FLC measured at 3 months after SCT. Though normalization of serum immunofixation and kappa–lambda ratio (KLR) correlated, a normal KLR was not associated with prolonged progression-free survival (PFS) or overall survival (OS).[21] In contrast, Mori et al studied 73 patients and found that relative to bone marrow aspiration and biopsy, the addition of FLC to M-spike at diagnosis and after induction with novel therapies (and before SCT) improved the accuracy of response assessment, including associated improvements in PFS and OS after SCT.[22] The reason for the disagreement in these 2 studies is unclear but may be related to different induction regimens or timing of FLC measurement (VAD vs. novel agents and 3 months after SCT vs. before SCT, respectively).

In this retrospective study, given the relatively short half-life of FLC, we examined the ability of FLC measured early in the post-SCT period to identify patients at risk of early relapse and to predict long-term PFS and OS. Our study differs from prior studies by having FLC measured early after SCT and the ability to compare these values to pre-SCT measurements.

Patients and Methods

We retrospectively reviewed the records of patients treated at the MM program at the St Vincent's Comprehensive Cancer Center and upon closure of the same at the Mount Sinai School of Medicine with patients with MM who received an autologous SCT from June 2009, when we began routinely measuring FLC early after SCT (in addition to serum and 24-hour urine electrophoresis) through November 2011. Patients were included in the study if they received intermediate- or high-dose chemotherapy (melphalan $\geq$ 100 mg/m^2) with autologous stem cell support and had FLC measurements early after SCT, defined as within 2 months. Multiple SCTs from the same patient could be included as consolidation after induction, as consolidation of a salvage regimen, or as a salvage treatment at the time of disease progression. Patients who underwent allogeneic transplantations were excluded.

Patients received a complete restaging, including a bone marrow biopsy/aspirate when indicated, at 3 months after SCT. High-risk cytogenetic or fluorescence in-situ hybridization (FISH) abnormalities were defined as deletion 13, deletion 17p, t(4;14), or t(14:16). Response to treatment was assessed according to the International Myeloma Working Group (IMWG) uniform response criteria.[23] This study was approved by the Mount Sinai School of Medicine's institutional review board.

PFS and OS were calculated from the day of stem cell infusion by the Kaplan-Meier method. Comparisons at the univariate level were made by the log rank test, and multivariate analysis was performed by a Cox proportional hazard model. Statistical analyses were performed by IBM SPSS Statistics, version 20.

Results

Of 83 consecutive MM patients who had an autologous SCT, 69 (83%) had serial FLC measurements enabling comparison between pre- and post-SCT values and were included. Their baseline characteristics are summarized in Table 1. The median age was 59 years, and approximately half received the SCT as consolidation during their first line of therapy. Of those who received it as a second line or higher therapy, it was a median third line of therapy (range, second to 11th), and 23 of these 38 patients entered SCT with progression of disease. Two patients were included in the database twice for separate SCTs. The median duration of follow-up from time of SCT was 335 days. At the time of SCT, only 33% had measurable M-spike of at least 0.5 g/dL, but 77% had abnormal KLR.

As per the inclusion criteria, all patients had FLC measured early after SCT, with 71% measured at approximately day 30 (D30) and 80% at D60 after SCT. One potential use of measuring FLC early after SCT is to identify patients at risk of early relapse. To identify these patients, we compared the difference between involved and uninvolved FLC (dFLC) measured at 3 different time points: D30 versus pre-SCT, D60 versus pre-SCT, and D60 versus D30. Pre-SCT FLC were values measured within 30 days before SCT and after all induction chemotherapy had already been provided.

Because not all patients had FLC measured at both D30 and D60, we considered patients at increased risk of early relapse if by D30 or D60 they either failed to experience at least a PR by conventional FLC criteria (ie, a 50% reduction in dFLC for those with a pre-SCT value of 100 mg/L or more) or alternatively those who experienced progression early by FLC (ie, a 25% increase in dFLC and an absolute increase of at least 100 mg/L).[23] Six patients did not experience an early PR by FLC, and an additional 2 patients had early disease progression by FLC. Of these 8 patients, 1 received SCT as consolidation of first-line therapy, 2 received SCT as consolidation a second or higher line of therapy, and 5 received a salvage SCT at time of disease progression.

Kaplan-Meier estimates of median PFS were 98 days for these 8 high-risk patients compared to 335 days for the remaining patients (Figure 1A, $P = .001$). Although median OS had not been reached for the standard-risk group, the high-risk group had a statistically significant shorter OS (Figure 1B, $P = .016$). Of note, there were no other clinical symptoms or signs of progression, and the FLC

Table 1 Patient Characteristics

Characteristic	Value
Age, years, median (range)	59 (35-71)
Gender (% male)	61
Renal failure (n)	1
Myeloma isotype (n)	
IgG	34
IgA	10
IgM	1
IgD	2
Light chain	22
Newly diagnosed (%)	43
Prior lines of therapy, median (range)	1 (0-11)
Role of SCT (n)	
Consolidation of first-line treatment	31
Consolidation of more than first-line treatment	15
Salvage at time of disease progression	23

Abbreviation: SCT = stem cell transplantation.