Clinical Chemistry 55:8
1510–1516 (2009)

Serum Free Light Chain Ratio, Total κ/λ Ratio, and Immunofixation Results Are Not Prognostic Factors after Stem Cell Transplantation for Newly Diagnosed Multiple Myeloma

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BACKGROUND: The prognostic value of changes in paraprotein markers after stem cell transplantation is unknown. We evaluated disease response using serum immunofixation (s-IFIX), total κ and λ ratio (KLR), and free light chain (FLC) ratio in myeloma patients who underwent autologous or autologous plus allogeneic stem cell transplantation.

METHODS: We studied s-IFIX, KLR, and FLC ratio in sera from 203 patients, 3 months after transplantation. We evaluated overall and event-free survival (OS and EFS, interval between date of study enrollment and date of death from any cause or date of progression, relapse, or death from any cause, respectively) by the Kaplan–Meier method.

RESULTS: Of the 203 patients, 51 were negative by s-IFIX, 99 reached a normal KLR, and 92 had a normal FLC ratio. Of the 51 patients with negative s-IFIX, 40 (78%) also had a normal FLC ratio. The median duration of OS was 54.3 months, and the median EFS was 19.5 months. None of the measured paraprotein parameters showed an association with OS. Only a normal KLR was associated with prolonged EFS ($P = 0.016$). Even a negative s-IFIX associated with a normal FLC ratio did not show a significant difference in terms of EFS and OS.

CONCLUSIONS: Our analysis with a small cohort of patients did not show a significant impact of achieving complete response (CR) or stringent CR on patient survival.

Immunonephelometric assays for serum κ and λ light chains [free light chains (FLCs)[3]] circulating as monomers or dimers were developed in 2001 *(1)*. These tests have minimal cross-reactivity with whole immunoglobulins and no reactivity with the other light chain. Quantification of the κ and λ FLCs and calculation of the serum FLC (sFLC) ratio have been reported to be diagnostically sensitive and specific for detection of excess monoclonal FLCs. The usefulness of sFLC in disease diagnosis and early treatment response in multiple myeloma (MM) and primary systemic amyloidosis (AL) has been demonstrated *(2–7)*. In particular, in some patients with nonsecretory myeloma and amyloidosis, sFLC assays have allowed the detection of monoclonal proteins that were previously undetectable *(2, 6)*. By virtue of the short half-lives of sFLC compared with intact immunoglobulins, this measurement also provides a rapid indication of response to treatment *(8)*.

It was recently suggested that sFLC baseline values have prognostic relevance. In particular, in monoclonal gammopathy of undetermined significance (MGUS) *(9)*, smoldering myeloma *(10)*, and solitary plasmacytoma *(11)*, an abnormal sFLC ratio was associated with a higher risk of progression to MM. In newly diagnosed AL amyloidosis and MM, baseline FLC values, measured before initiation of any treatment or transplantation, were predictive of survival *(12–15)*.

Furthermore, the new international consensus for the management of AL amyloidosis *(16)* and the new international response criteria for myeloma *(17)* incorporated the FLC assay to define complete remission

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Received February 2, 2009; accepted May 28, 2009.
Previously published online at DOI: 10.1373/clinchem.2009.124370
[3] Nonstandard abbreviations: FLC, free light chain; sFLC, serum FLC; MM, multiple myeloma; AL, amyloidosis; MGUS, monoclonal gammopathy of undetermined significance; CR, complete remission; sCR, stringent CR; PR, partial response; SCT, stem cell transplantation; KLR, κ/λ ratio; s-IFIX, serum immunofixation; EFS, event-free survival; OS, overall survival; VAD, vincristine, doxorubicin, and dexamethasone; G-CSF, granulocyte colony-stimulating factor; Mel, melphalan; PPV, positive predictive value; NPV, negative predictive value; PFS, progression-free survival; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, and prednisone.

Table 1. Patient characteristics.[a]

Age, years	56 (33–74)
Follow-up, months	37 (10–117)
Patients	203
Male	110
Female	93
Myeloma type and isotype	
IIMM[b]	154
IgG	105
IgA	47
IgM	1
IgD	1
LCMM	47
κ	24
λ	23
NSMM	2

[a] Data are median (range) or n.
[b] IIMM, intact immunoglobulin multiple myeloma; LCMM, light chain multiple myeloma; NSMM, nonsecretory multiple myeloma.

(CR) in AL, stringent CR (sCR) in MM, and partial response (PR) in patients affected by MM with "unmeasurable disease." Nevertheless, a controversy still exists related to the impact of depth of hematologic response after chemotherapy or stem cell transplantation (SCT) on subsequent outcomes in MM *(18–23)*.

We investigated, in a retrospective analysis, the prognostic value of achieving a normal sFLC ratio, normal total κ/λ ratio (KLR), and negative serum immunofixation (s-IFIX), on event-free survival (EFS) and overall survival (OS) in a cohort of MM patients who underwent autologous stem SCT or tandem autologous and allogeneic SCT.

Materials and Methods

PATIENTS

From July 1995 to February 2006, 203 patients (median age 56 years) with newly diagnosed MM *(24)* entered the study. In the current analysis, 154 patients had intact immunoglobulin monoclonal proteins typed by s-IFIX (105 IgG; 47 IgA; 1 IgM; 1 IgD); 47 had light chain MM (51% κ; 49% λ) with Bence Jones proteins quantified nephelometrically, typed by urine immunofixation, and with positive light chains by s-IFIX. In addition, sera from 2 patients with nonsecretory MM were studied. Other characteristics of the population are shown in Table 1.

Informed consent was obtained in accordance with the Declaration of Helsinki.

Table 2. Treatment details.[a]

Auto SCT	173 (85)
Single	15 (9)
High-dose Mel	5 (33)
Intermediate-dose Mel	10 (67)
Double	145 (84)
High-dose Mel	69 (48)
Intermediate-dose Mel	76 (52)
Triple, intermediate-dose Mel	13 (7)
Tandem auto-/allogeneic SCT	30 (15)

[a] Data are n (%). Median time from diagnosis to first SCT was 7 months (range 3–57 months).

TREATMENT DETAILS

Treatments for these patients are summarized in Table 2. The 15 patients who underwent a single autologous SCT received induction chemotherapy with 2 or 3 courses of vincristine, doxorubicin, and dexamethasone (VAD). Peripheral blood stem cells mobilized by 3–4 g/m^2 of cyclophosphamide and granulocyte colony-stimulating factor (G-CSF) were collected after the patient had recovered from VAD treatment. The autograft was administered after a high (200 mg/m^2) or intermediate (60–120 mg/ m^2) dose of melphalan (Mel). The 145 patients treated with double autologous SCT underwent the same induction treatment and mobilization followed by 2 courses of a high (140–200 mg/m^2) or intermediate (60–120 mg/m$^{2)}$ dose of Mel, 2–3 months apart. All 13 patients who had 3 consecutive autologous SCTs were conditioned with intermediate (50–120 mg/m^2) doses of Mel. Thirty patients with a HLA-identical sibling received an autologous SCT with Mel 200 mg/m^2 followed by nonmyeloablative total-body irradiation (2 Gy) and allogeneic transplant *(25)*.

RESPONSE CRITERIA

Response criteria were those proposed by the European Group for Blood and Marrow Transplant *(26)* and the International Myeloma Working Group *(17)*. Thus, patients were considered in CR if they had a negative s-IFIX and blood marrow plasma cells ≤5% at the time of response evaluation; patients in sCR also had a normal sFLC ratio. The response was evaluated 3 months after the last transplant.

ASSAY METHODS

We measured FLC concentrations in serum using the Freelite™ assay (The Binding Site) performed on a Beckman Coulter IMMAGE™ nephelometer. This test

Table 3. Laboratory results.

	Normal sFLC ratio and normal KLR (n = 64)	Normal sFLC ratio and abnormal KLR (n = 28)	Abnormal sFLC ratio and normal KLR (n = 35)	Abnormal sFLC ratio and abnormal KLR (n = 76)
s-IFIX positive (n = 152)	27	25	24	76
s-IFIX negative (n = 51)	37	3	11	0

can detect as little as 3.0 mg/L of free κ and 4.0 mg/L of free λ light chain *(27)*. We compared results with FLC reference ranges derived from 282 normal individuals aged 20–90 years: free κ 3.3–19.4 mg/L, free λ 5.7–26.3 mg/L, and sFLC κ/λ ratio 0.26–1.65 *(28)*. Patients with sFLC ratios <0.26 are typically defined as having a monoclonal λ FLC and those with ratios >1.65 as having a monoclonal κ FLC. We assessed total κ and λ by nephelometry on the Beckman Coulter IMMAGE; the anti-κ and anti-λ antisera used in this assay reacted against both FLC and light chains in intact immunoglobulins. Normal serum values of κ and λ in a population without monoclonal or polyclonal gammopathies were κ, 6.29–13.2 g/L; λ, 3.53–7.07 g/L; KLR, 1.1–2.9 *(29)*. We performed high-resolution immunofixation on serum samples with a modified method of the Sebia Hydragel kits on the Sebia Hydrasys electrophoresis system (Sebia), using agarose gels (sensitivity 150–500 mg/L) *(30)*. Serum samples were considered positive when a monoclonal band was present on agarose gel.

STATISTICAL ANALYSIS

The primary study endpoints were to evaluate, by univariate analysis, the variables total KLR, sFLC ratio, and s-IFIX for OS and EFS. OS was calculated from date of study enrollment (median 3 months posttransplant, range 1–5 months) to date of death from any cause; EFS was estimated from date of study enrollment to date of disease progression (increase ≥25% from baseline in serum M-component and/or urine M-component), relapse, or death from any cause *(17)*. Secondary study endpoints included OS and EFS in sCR patients and in patients negative for all 3 parameters (negative s-IFIX, normal KLR, normal sFLC ratio). We plotted curves for OS and EFS according to the Kaplan–Meier method and compared them using the log-rank test. Hazard ratios were estimated by univariate models, and groups were compared with the log-rank test; moreover, to exclude confounding results due to varying treatments and varying clinical support over the time interval, we conducted a multivariate analysis using the Cox proportional hazard regression *(31)*.

We evaluated the relationship between KLR and FLC ratio using Pearson correlation analysis and used χ^2 test for categorical data analysis. Positive and negative predictive values (PPV and NPV) were calculated for KLR and sFLC ratio using s-IFIX as the gold standard.

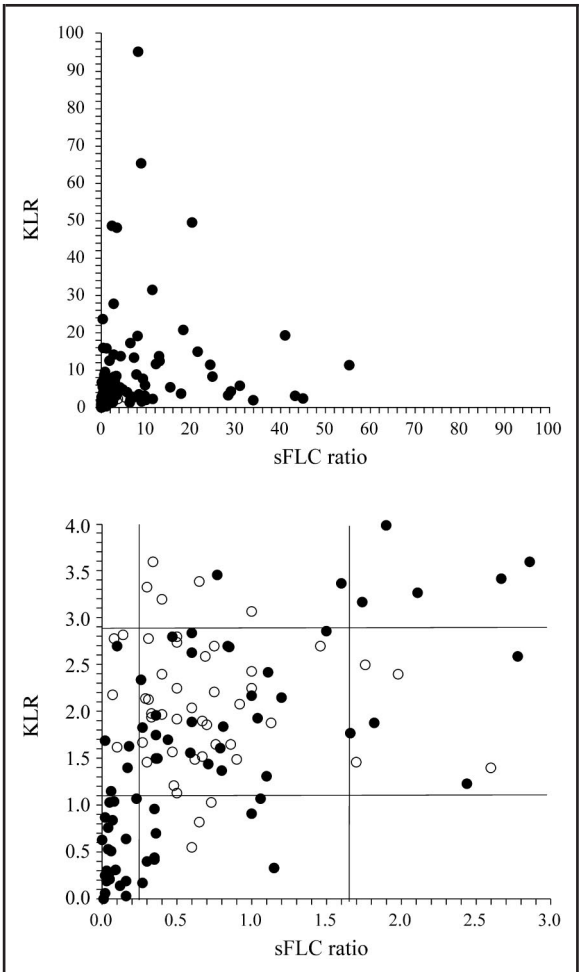

Fig. 1. Top: sFLC ratio versus KLR for 203 multiple myeloma patients.

Bottom: sFLC ratio versus KLR for patients with normal or borderline values. Vertical lines, sFLC ratio cutoff values; horizontal lines, KLR cutoff values; ●, s-IFIX positive; ○, s-IFIX negative.

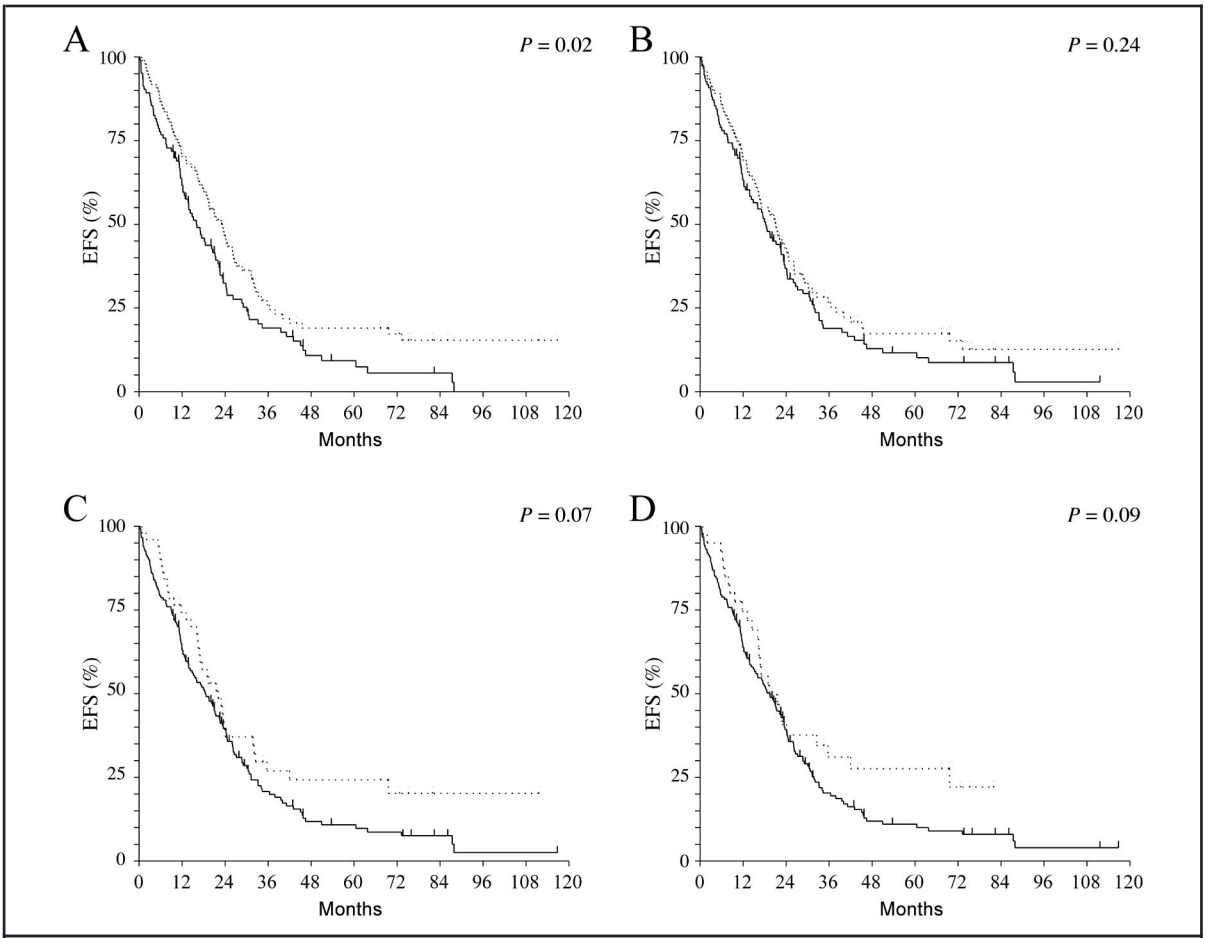

Fig. 2. Kaplan–Maier estimates of EFS.

(A), Patients with normal (dotted line) and abnormal (solid line) KLR. (B), Patients with normal (dotted line) and abnormal (solid line) sFLC ratio. (C), Patients with negative (dotted line) and positive (solid line) immunofixation. (D), Patients in sCR (dotted line) and not in sCR (solid line).

Results

LABORATORY RESULTS

Of the 203 patients, 51 became negative for s-IFIX and were considered in CR, 99 patients reached a normal KLR and 92 had a normal sFLC ratio. Forty patients had a negative s-IFIX with a normal sFLC ratio and reached sCR.

As shown in Table 3, 52 patients with a normal sFLC ratio had a positive s-IFIX. Furthermore, all but 11 of 111 patients with an abnormal sFLC ratio were positive for s-IFIX (90% positive s-IFIX). A statistically significant connection ($\chi^2 = 28.3$, df = 1) between s-IFIX and sFLC ratio was observed ($P < 0.0001$). The PPV and NPV were 90% and 43%, respectively.

Ninety-nine patients achieved a normal total KLR. Among these, the s-IFIX results were equally distributed, 48 patients being negative and 51 remaining positive, whereas all but 3 of 104 patients with abnormal KLR were positive for s-IFIX ($P < 0.0001$). PPV and NVP were 97% and 48%, respectively.

Sixty-four patients with normal KLR had a normal sFLC ratio, whereas 35 patients with a normal KLR had an abnormal sFLC ratio. Among 104 patients with abnormal KLR, 76 patients (73%) also had an abnormal sFLC ratio, whereas 28 patients (27%) had a normal sFLC ratio. There was a poor correlation between KLR and sFLC ratio ($r = 0.058$, $P = 0.4$). Finally, 37 patients were negative for all 3 parameters (negative s-IFIX, normal KLR, normal sFLC ratio) (Table 3, Fig. 1).

EFS AND OS

Overall, the median duration of EFS and OS was 19.5 months (95% CI 16.3–22.6 months) and 54.3 months

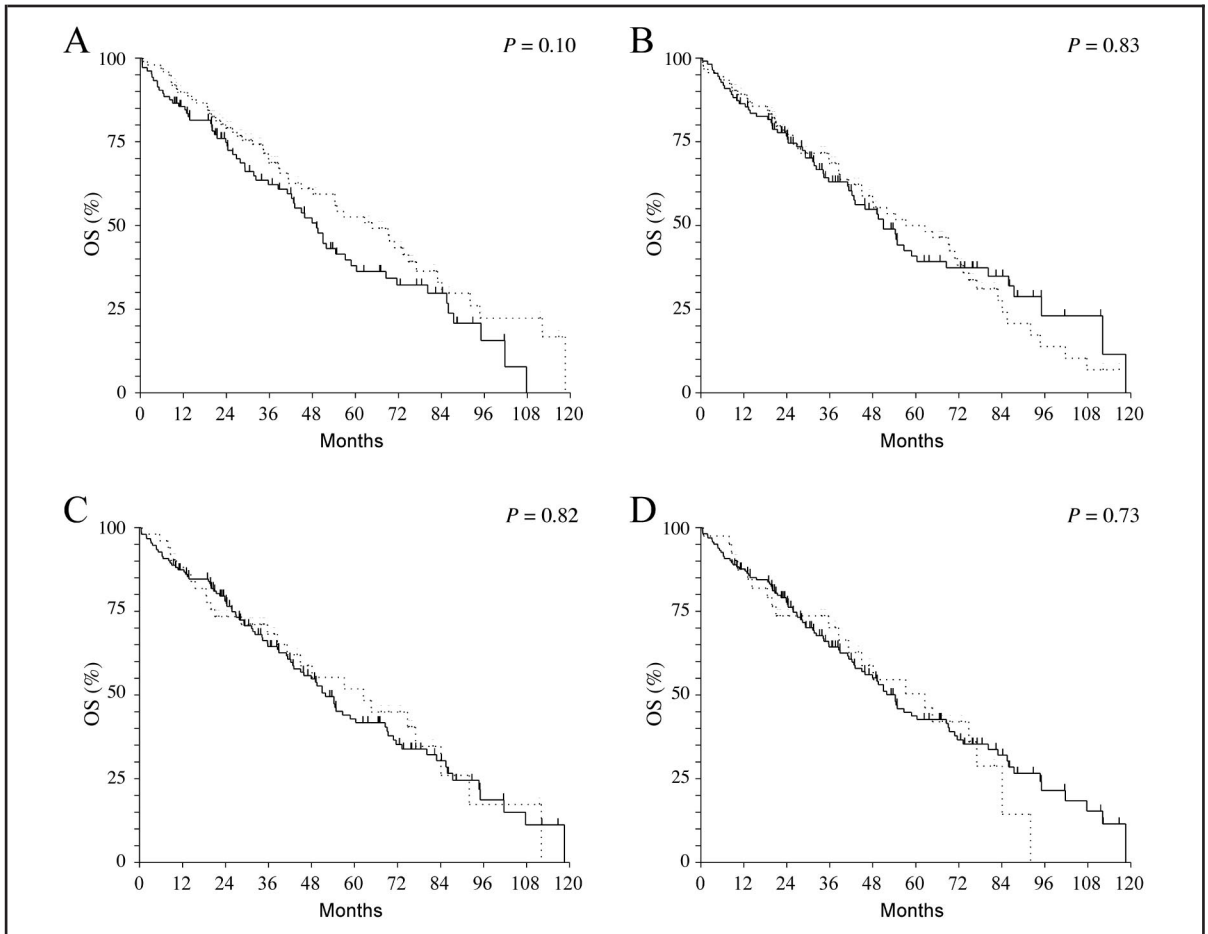

Fig. 3. Kaplan–Maier estimates of OS.

(A), Patients with normal (dotted line) and abnormal (solid line) KLR. (B), Patients with normal (dotted line) and abnormal (solid line) sFLC ratio. (C), Patients with negative (dotted line) and positive (solid line) immunofixation. (D), Patients in sCR (dotted line) and not in sCR (solid line).

(45–64.7 months), respectively. Interestingly, achieving a normal KLR 3 months after SCT significantly prolonged the EFS (hazard ratio 0.68, 95% CI 0.50–0.93, $P = 0.02$), whereas a normal KLR did not affect OS ($P = 0.10$) (Figs. 2A and 3A). Patients achieving a negative s-IFIX and therefore CR 3 months after SCT did not show any survival benefits in terms of both EFS and OS ($P = 0.07$ and $P = 0.81$, respectively) (Figs. 2C and 3C). Similarly, a normal sFLC ratio 3 months after SCT did not translate into an improvement in EFS and OS ($P = 0.24$ and $P = 0.83$, respectively) (Figs. 2B and 3B).

We evaluated the outcome of patients achieving sCR (normal IFIX and sFLC ratio), and in agreement with previously published studies *(15)*, we did not observe any advantage in terms of EFS and OS ($P = 0.09$ and $P = 0.73$, respectively) (Figs. 2D and 3D). Furthermore, the normalization of all serum parameters (KLR, sFLC ratio, and s-IFIX) did not confer any significant benefit in terms of EFS and OS ($P = 0.07$ and $P = 0.70$, respectively). Also using multivariate analysis, including the year of diagnosis and high-dose therapy as covariates, sCR did not correlate with improved EFS.

Discussion

The impact of CR in long-term outcome of MM patients is still a matter of debate. Studies comparing single vs double autologous SCT reported a superior near-CR (IFIX positive, electrophoresis negative) or CR rate in double autologous SCT, translating into a longer EFS. Nevertheless, these observations did not consistently translate into an improved OS *(18, 22)*. Lahuerta et al. *(32)*, however, recently reported a significant correlation between posttransplantation qual-

ity of response, notably CR, and prolonged EFS and OS in newly diagnosed patients with MM. All these studies were based on s-IFIX to evaluate the response after SCT, and none of them evaluated sCR. The new sFLC immunoassays have detection limits >50-fold lower than electrophoresis and approximately 20-fold lower than immunofixation *(1)*. Although van Rhee et al. *(13)* observed that increases in baseline sFLC values were associated with poorer progression free survival (PFS) and OS, there has been no data to document that sCR response is prognostic for EFS or OS after SCT.

We explored, in a retrospective analysis, the predictive role of a normal sFLC ratio, a normal KLR, and a negative s-IFIX in defining the outcome of MM patients, treated at diagnosis with SCT. Similar to other studies, our analysis was restricted to only 1 time point after treatment. With the limitation of a relatively small cohort of patients (n = 203), we observed that the achievement of CR, sCR, or normal results for all parameters, 3 months after intermediate or high-dose melphalan followed by autologous or tandem autologous and allogeneic SCT, did not confer any survival advantage. In multivariate analysis, the year of diagnosis and the dose of melphalan did not have any impact on EFS of patients in sCR, suggesting that the results were not affected by varying treatments and by varying clinical support over the time interval. An apparent benefit on EFS, but not on OS, was observed with achievement of a normal KLR. We speculate that reaching a normal KLR could be sufficient to maintain a stable phase of the disease characterized by a later incidence of relapse.

Our results are in agreement with Dispenzieri et al. *(15)*, who demonstrated that sFLC response after 2 months of VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, and prednisone) treatment did not predict for OS or PFS. We showed the absence of a correlation between KLR and sFLC ratio, and that KLR and sFLC ratio were variables independent of each other. These findings could explain the different impact on survival between KLR and sFLC ratio observed in our study. We also demonstrated that, 3 months after the last autologous or tandem autologous and allogeneic SCT, a continuing abnormal KLR or sFLC ratio could statistically predict a positive s-IFIX. On the contrary, reaching a normal KLR or sFLC ratio could not assure a negative s-IFIX, namely a CR condition.

These results should be validated in a larger cohort of patients and in a prospective study with the use of novel agents such as thalidomide, bortezomib, and lenalidomide, which are currently included in most of the newer SCT trials *(33–35)*. Indeed, the impact of new drugs might change the role of the quality of response in patient survival.

Author Contributions: *All authors confirmed they have contributed to the intellectual content of this paper and have met the following 3 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; and (c) final approval of the published article.*

Authors' Disclosures of Potential Conflicts of Interest: *Upon manuscript submission, all authors completed the Disclosures of Potential Conflict of Interest form. Potential conflicts of interest:*

Employment or Leadership: None declared.
Consultant or Advisory Role: None declared.
Stock Ownership: None declared.
Honoraria: None declared.
Research Funding: (*a*) Regione Piemonte: Ricerca Scientifica Applicata 2004; (*b*) The Binding Site LTD; and (*c*) Progetti di Ricerca (Progetti di Ricerca represents 60% of university funding).
Expert Testimony: None declared.

Role of Sponsor: The funding organizations played a direct role in the final approval of manuscript.

Acknowledgments: Our thanks to Federica Leotta for her technical assistance.

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