Monitoring serum free light chains in patients with multiple myeloma who achieved negative immunofixation after allogeneic stem cell transplantation

Monitoring of serum free immunoglobulin light chains (FLC) in 26 myeloma patients who achieved immunofixation negativity after allografting showed a decrease of FLC at a median of 128 days before immunofixation negativity. In patients who subsequently relapsed, a 25% increase of FLC was observed at a median of 98 days before immunofixation positivity.

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The quantitative assay for free light chains (FLC) has been reported to be sensitive and specific for detecting and monitoring FLC diseases produced by monoclonal gammopathies, such as multiple myeloma,[1-4] monoclonal gammopathies of undetermined significance,[5,6] and amyloidosis.[7] The potential advantages of measuring FLC in serum are i) the shorter serum-half-life in comparison to intact immunoglobulin, and ii) that it can show abnormal serum levels despite normal electrophoresis.[3] We evaluated the kinetics of FLC and κ/λ ratios in 26 patients with multiple myeloma who achieved negative immunofixation after dose-reduced allogeneic stem cell transplantation, as recently described.[8]

The study included 19 male and 7 female patients with a median age of 53 years (range: 31 – 62 years). Myeloma was classified as Bence-Jones-κ (n=5) or -λ (n=4), IgGκ (n=8), IgGλ (n=3), IgAκ (n=3) and IgA (n=3). FLC measurements were performed with the commercially available Freelite™ kit (Binding Site, Heidelberg, Germany). Normal ranges in serum are: κFLC=3.3–19.4 mg/L; λFLC=5.71–26.3 mg/L; κ/λ ratio=0.26–1.65.

The patients could be divided into three groups on the basis of changes in immunofixation status.

Group 1 consisted of 12 patients who remained immunofixation-negative during a follow-up of a median of 19 months (range: 5–30 months). Eighty-one FLC measurements (77 %) showed normal results, while 24 measurements (23 %) were above the normal range. Eleven of these elevated results (median λ: 42.1 mg/L) originated from a single patient with an IgAκ-myeloma. The other 13 measurements above the normal range were only modestly elevated (median: 24.9 mg/L and median λ: 31.4 mg/L).

κ/λ-ratio data showed 99 measurements (94 %) within the normal range and 6 (6 %) out of the normal range. Three of the six abnormal κ/λ ratios (results: 0.13, 0.14, 0.12) originated from the patient who also had 11 elevated λ-FLC-measurements (see above). The remaining three abnormal κ/λ ratios (results: 2.24, 2.1, 1.78) occurred only once and were not confirmed in subsequent measurements.

Group 2 consisted of nine patients who were immunofixation-negative but became positive during a median follow-up of 23 months (range: 14-31 months).

At the time of negative immunofixation tests, all patients showed normal FLC concentrations and κ/λ ratios. In all patients, the relevant FLC increased to abnormal levels during follow-up. Eight of the patients also showed abnormal κ/λ ratios but in one patient the κ/λ ratio remained within the normal range while FLC concentrations were elevated at the same time. A 25% increase of FLC or a 25% increase or decrease of κ/λ ratio was observed at a median of 98 days (range of FLC: 35-238 days; range of κ/λ ratio: 35-219 days) before immunofixation became positive (Figure 1) While changes in the κ/λ -ratio and FLC concentrations have been shown to reflect disease progression in light-chain myeloma,[1] no clear correlation has been reported so far for patients with intact immunoglobulin protein. Despite the fact that circulating FLC are present in more than 95% of patients with multiple myeloma,[3] Tate *et al.*[9] reported on six out of 11 patients with intact immunoglobulin protein who had a normal FLC ratio at or prior to disease relapse. In other series, FLC were reported to be an early indicator of disease progression in only 15 % of the patients.[3,10]

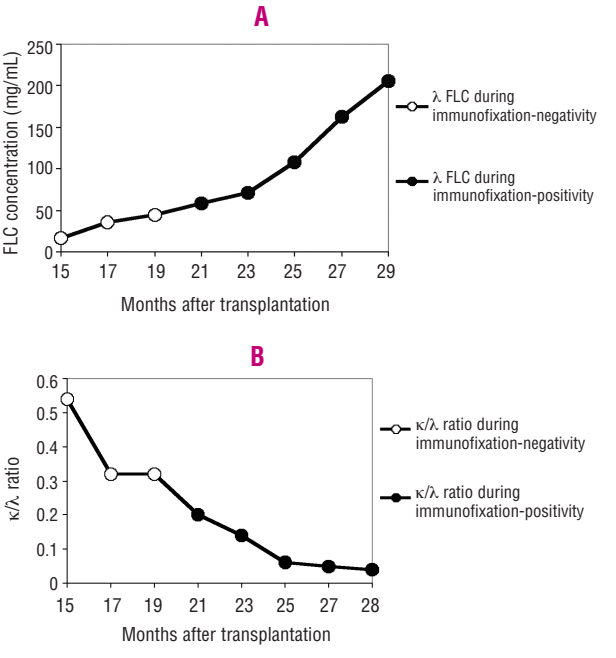

Figure 1. Representative example of FLC (A) and κ/λ ratio (B) of a patient with Bence-Jones-λ-myeloma, who became immunofixation-positive during follow up (normal range for FLC λ (λ): 5.71 – 26.3 mg/L; for κ/λ (κ/λ) ratio 0.26 - 1.65)

Group 3 consisted of five patients who achieved near complete remission with still positive immunofixation after allogeneic stem cell transplantation and became immunofixation-negative during a median follow-up of 23 months (range: 18–31 months). While immunofixation-positive all patients showed elevated FLC levels. In all patients a decrease of FLC of at least 25 % appeared at a median of 128 days (range: 77–217 days) before immunofixation-negativity (Figure 2). At the time of the first negative immunofixation, all patients showed normal FLC levels and a normal κ/λ ratio.

Only three of the five patients showed abnormal κ/λ ratios while immunofixation-positive. An increase or decrease (depending on the relevant FLC) of at least 25% appeared at a median of 128 days (range: 77-140 days) before immunofixation became negative. In the other two cases monitoring of FLC started only approximately 3 months before immunofixation became negative thereby probably missing the time window in which a change in κ/λ ratio would have been observed. This result confirms several studies that have shown that FLC levels reflect tumor killing more rapidly than quantification of

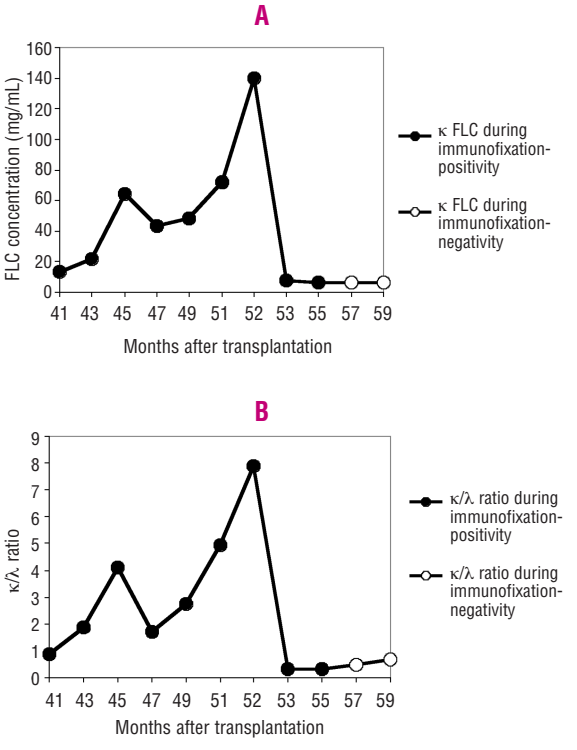

Figure 2. Representative example of FLC (A) and κ/λ ratio (B) of a patient with IgGκ-myeloma, who became immunofixation-negative during follow up (normal range for FLC κ (κ): 3.3–19.4 mg/L, for κ/λ (κ/λ) ratio 0.26–1.65).

intact immunoglobulin.[2,3] Unlike immunofixation, which is only quantitative, measurements of FLC levels allows to monitor the dynamics of paraprotein levels.

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