28.5. Patients with low amyloidogenic FLCs have distinct clinical features

Up to 20% of AL amyloidosis patients have a low sFLC burden at diagnosis (dFLC <50 mg/L), and have historically been excluded from clinical trials because no haematological response criteria besides a complete response (CR) can be applied to them [1]. Two initial European studies [1][2] published in parallel characterise the distinct clinical features and outcomes of these so-called ‘low dFLC’ patients, and two further studies [3][4] further build on these findings. Milani et al. [2] compared 203 newly diagnosed low dFLC patients with 866 patients with measurable sFLCs, and found that low dFLC patients had a smaller plasma cell clone than those with measurable disease (median bone marrow plasma cell infiltrate 8% vs. 12%, p<0.001). This finding was confirmed by others [1][3][4], who also reported no significant difference in the frequency of cytogenetic abnormalities between the two groups [1][3].

Patients with low dFLC have a more favourable outcome compared to those with evaluable FLCs, regardless of treatment type [1][2][3][4]. For example, Milani et al. [2] reported a median overall survival of 118 months for patients with low dFLC, compared to 21 months for measurable patients (p<0.001). Although renal involvement was slightly higher (77% vs. 63%, p<0.001) and more severe in the low dFLC group, heart involvement was less common (43% vs. 83%, p<0.001) and less severe. Similar findings were reported by Sidana et al. [3], who also demonstrated that in multivariate analysis (that included dFLC, 24-hour urine protein, renal function, and cardiac biomarkers), dFLC (<50 mg/L) was an independent predictor of survival. These findings were confirmed by others [1][2][4].

Dittrich et al. [1] proposed a new low-dFLC partial response (PR), defined as a reduction of dFLC to below 10 mg/L (provided that dFLC was 20-50 mg/L at baseline). After 6 months of therapy, low dFLC patients who achieved a PR had a superior outcome compared to those who did not (median overall survival not reached vs. 92 months, p=0.004). The low-dFLC response criteria were subsequently validated by a number of other groups [2][3][4]. Milani et al. [2] also reported a prognostic benefit for low-dFLC patients who achieved an amyloid CR. However this was not confirmed by Dittrich et al. [1], who commented that the discrepancy may be due to differences in the sensitivity of immunofixation electrophoresis methods used by the two centres, and further supports the application of FLC assays in response assessment. Rezk et al. [5] have proposed alternative FLC response criteria, based on the percentage reduction in dFLC, regardless of the initial concentration and Sidana et al. [3] demonstrate that normalisation of involved FLC levels is also predictive of overall survival. Further validation of these new sFLC response categories is now required.
At disease relapse, dFLC levels are generally lower than at presentation. Palladini et al. [6] characterised 92 AL amyloidosis patients at the time of second-line therapy initiation. The median dFLC was 55 mg/L, and corresponded to 41% of the baseline value. Importantly, 48% (44/92) subjects were classed as non-measurable, but when the new threshold for assessing low-dFLC response (20 mg/L) was considered, 81% had measurable disease.

In conclusion, the subgroup of AL amyloidosis patients with low dFLC at baseline represents a distinct clinical entity with an excellent prognosis, and at disease relapse many additional patients are classified as non-measurable. It is hoped that new low dFLC response criteria will improve the clinical management of these patients and allow the majority of them to be included in future clinical trials.

References


