Various studies have highlighted the prognostic significance of both the depth and rate of sFLC response following treatment of MM. In addition, patients relapsing with FLC production appear to have an adverse prognosis. These aspects are now considered separately.

### 20.3. Normalisation of the sFLC ratio and importance of a sCR

The latest IMWG consensus criteria for response and minimal residual disease (MRD) assessment in MM include a stringent complete response (sCR) category, which requires normalisation of a sFLC ratio in addition to other criteria (Sections 18.2.2 and 25.3.5).

Kapoor et al. reported the largest study of the prognostic value of a sCR in 445 patients who underwent an autologous stem cell transplant (ASCT) within 12 months of MM diagnosis. Five-year overall survival (OS) for patients with a sCR (n=109), conventional CR (n=37) and “near CR” (nCR; n=91) was 80%, 53% and 47% respectively. Progression-free survival (PFS) and OS curves are shown in Figure 20.5 A and B. It was also observed that OS was superior in patients who maintained their sCR status for at least 6 months compared to those who had a sCR which was maintained for less than 6 months (Figure 20.5). The authors concluded that myeloma trials reporting response rates should identify those achieving sCR and conventional CR separately owing to their markedly disparate outcomes. Other studies have also reported a prognostic benefit of sFLC ratio normalisation in patients who achieve a CR.

Conflicting data on the prognostic value of the $\kappa/\lambda$ sFLC ratio at CR have been reported. For example, Jiménez Ubieto et al. reported no survival benefit of $\kappa/\lambda$ sFLC ratio normalisation in 203 MM patients who achieved a CR in Spanish PETHEMA clinical trials. Similar findings were reported by others. Pratt et al. discuss a possible explanation for why these observations are contradictory to the findings of Kapoor et al. The Spanish group analysed a smaller population of patients in CR (n=94) and utilised EBMT criteria, whereas Kapoor et al. analysed a large cohort (n=445) using IMWG response criteria. Given that a CR according to EBMT is stricter than IMWG (IFE negativity must be sustained for at least 6 weeks), this may explain why outcomes for patients in CR versus sCR were similar in the Spanish study.

Several studies suggest a prognostic role of sFLC ratio normalisation in IMWG response categories other than CR. Iwama et al. reported that sFLC ratio normalization identified patients with improved OS and PFS whether they had achieved a conventional CR, a very good partial response (VGPR) or a partial response (PR) (n=126; p<0.001). Similar results were reported by Tacchetti et al., Matsue et al. and Yagci et al. However, these studies did not look at patients with LCMM or IIMM separately.

In a study of LCMM patients only (n=122), those who normalised both their $\kappa/\lambda$ sFLC ratio and iFLC values had significantly longer PFS and OS compared to patients that normalised their ratio only. Both these groups had better survival than those
failing to normalise either parameters (median PFS: 43.3, 33.0 vs. 18.8 months, respectively [p<0.001]; median OS: 85.3, 69.9 vs. 45.5 months, respectively [p=0.012]). Similar findings were reported by others [17][18]. Dejoie et al. [17] confirmed the prognostic utility of sFLC measurements in LCM-MM, both in early responders (after 3 treatment cycles) as well as in those patients whose sFLC parameters normalise later during monitoring. Importantly, all patients whose sFLC ratio normalised after 1 or 3 cycles went on to achieve MRD negativity by flow cytometry. The study also compared the prognostic value of the serum vs. urine FLC response, which is discussed further in Section 24.8.

Moustafa et al. [19] studied the prognostic significance of normalisation of the κ/λ sFLC ratio in IIMM patients with residual monoclonal intact immunoglobulin at the time of maximal response. The study included 449 newly diagnosed IIMM patients who achieved less than a CR at the time of first best response following therapy. Normalisation of the sFLC ratio was seen in 34% of patients, and was associated with a longer PFS and OS compared to that of patients with an abnormal sFLC ratio (PFS: 29 vs. 16 months, p<0.001; OS: 91 vs. 58 months, p<0.001). In a multivariate model, normalisation of the sFLC ratio remained prognostic, and the authors concluded that their findings support the inclusion of sFLC analysis in all levels of response criteria. Similar findings were reported by Abe et al. [20].

An alternative prognostic use of sFLC analysis was made by Singh and colleagues [21] who monitored the uFLC concentration in patients after reduced–intensity allogeneic transplant. Both uFLC and iFLC concentrations were suppressed immediately after transplant, and the patients (n=47) were divided into 3 groups according to whether their uFLC concentrations failed to recover, recovered early or recovered late. PFS was significantly longer in the late uFLC recovery group (median PFS not reached at 5 years vs. 11.8 months for early recovery and 4.6 months for no recovery; p=0.0001). The authors concluded that late uFLC recovery might indicate better graft versus MM effect and that monitoring uFLC may help in managing immune suppression strategies.

In addition to the sCR category, IMWG consensus criteria define MRD responses, based on flow cytometry, gene sequencing and imaging, for patients who have achieved a CR. Pratt et al. [22] propose that studies are designed to evaluate the best strategy to integrate these tests into routine practice. For example, sFLC analysis may prove useful to guide when MRD assessment is required; costly and invasive bone marrow biopsies could be restricted to patients with normal serum results.

## 20.3.2. Early sFLC response predicts outcome

The short serum half-life of FLCs means that concentrations can fall rapidly if therapeutic treatment has been successful (Section 18.3.1). A number of studies have investigated the prognostic implications of an early sFLC response.

Moritz et al. [23] assessed the prognostic value of changes in serum M-protein and sFLC measurements in 358 MM patients (n=85 newly diagnosed and 273 relapsed/refractory) with measurable disease (Section 25.3.5). Values were compared before and after the first treatment cycle, and categorised according to the degree of M-protein/sFLC reduction. Patients who had no response in either marker (M-protein: 87/358; dFLC: 117/358) were less likely to respond to treatment later on (both p<0.001) and had a shorter median survival (M-protein: 2.9 vs. 4.7 years, p<0.005; dFLC: 1.8 vs. 5.2 years, p<0.001) compared to patients with some degree of response. Importantly, greater decreases in M-protein and dFLC were associated with increased odds of better responses during the same treatment course and better overall survival. Similar findings reported in a study of 419 newly diagnosed MM patients [24]. These findings are in contrast to an early study by the same group [24], which did not show any survival benefit of the sFLC response. However, it should be noted that the therapy used in the earlier study did not include novel agents.

There is now overwhelming evidence that confirms the prognostic value of reductions in sFLCs following therapy. Such evidence has been published in various studies encompassing a number of different treatment modalities, including non-transplant patients [25][26][27] and transplant patients with measurements taken during/post induction therapy [28][29][30][31][32] and post ASCT [33][34], and also in relapsed/refractory patients [33][34][35].

## 20.3.3. Prognostic implications of relapse with FLCs

![Figure 20.6. Overall survival according to pa...](image-url)
Disease relapse characterised by an increase in sFLCs, with or without an associated increase in intact immunoglobulins, has been shown by several studies to be associated with worse patient outcomes.

For a MM patient with a monoclonal intact immunoglobulin at diagnosis, “light chain escape” or “FLC escape” is the term used to describe disease relapse with just monoclonal FLC production. This is examined in more detail in Section 18.2.1 but here, the prognostic implications of FLC escape are considered.

A study of 104 patients who relapsed after bortezomib-based salvage therapy found that 15 (14%) relapsed with an altered disease phenotype, of whom 9 (9%) had plasmacytoma/plasma cell leukaemia and 6 (6%) showed FLC escape. The transformed group had significantly worse median overall survival (10.7 vs. 32.7 months; p<0.001) (Figure 20.6). A separate investigation of relapse in 232 patients reported changes of immunoglobulin production in 39 (17%) patients, of whom 15 (6%) had FLC escape and 7 (3%) had monoclonal immunoglobulin escape. Both groups had similarly short survival after the change in production (approximately 3 months).

Brioli and colleagues have published the largest analysis of clonal change at relapse to date and reported that 10.4% (54/520) IIMM patients relapsed with FLC escape, 35.2% (183/520) relapsed with rising intact immunoglobulin plus FLC, while 49.6% (258/520) relapsed with significant rises in their intact immunoglobulin alone. Interestingly, they found that patients who relapsed with FLC alone or FLC plus immunoglobulin had similarly reduced survival after relapse compared to those without rising FLC (p=0.002; Figure 20.7). Tacchetti et al. reported FLC escape in a similar proportion of patients (10%). The authors also confirmed the prognostic significance of disease relapse characterised by an increase in sFLCs, with or without an associated increase in serum monoclonal protein. Increasing sFLCs predicted an imminent risk of progression with end organ damage in 70% of cases, and on multivariate analysis, an involved/uninvolved sFLC ratio ≥120 at relapse was an independent variable that predicted a shorter time to second progression (HR: 7.26). The authors conclude that these findings confirm the value of monitoring patients with sFLC measurements after treatment with novel agent-based therapies.

Disease relapse associated with significant increases in sFLCs can sometimes occur without signs and symptoms of end-organ damage. This is termed ‘biochemical relapse’ and was defined in IMWG consensus panel recommendations published by Rajkumar et al. For example, the definition of biochemical relapse by sFLC analysis requires an increase in iFLC by ≥200 mg/L (plus an abnormal sFLC ratio) in 2 consecutive measurements separated by ≤2 months. IMWG guidelines recommend that patients experiencing biological relapse alone do not necessarily need to be treated immediately. However, data from Katodritou et al. show that many clinicians prefer to start treatment at biochemical relapse. When they compared the outcomes of 207 MM patients who started therapy with lenalidomide/dexamethasone at either biochemical (n=140) or clinical relapse (n=67), they found that median PFS was significantly longer in patients treated at biochemical relapse than at clinical relapse (24 vs. 13.2 months, p=0.006). This difference remained significant after adjustment for other prognostic factors. Sidana et al. found a significantly increased median overall survival in patients treated at biochemical progression (n = 116) compared to patients treated at symptomatic relapse (n = 88) (125 vs. 81 months, p = 0.001). Importantly, the improvement in median overall survival for patients treated at biochemical relapse was conserved when compared to a small subset of patients (n=13) who were treated at clinical relapse but had prior biochemical relapse. Taken together, these data indicate that earlier therapeutic intervention before the development of symptomatic disease may lead to a more favourable outcome. These data may also indicate that current recommendations of adopting a "watch and wait" approach, with the intention of early identification of clinical relapse, may not offer any survival benefit.

In this study, 51% of patients who experienced loss of CR did not meet IMWG criteria for progression. 78% of these patients did eventually go on to progress as per IMWG criteria, and patients who lost CR due to an abnormal FLC ratio (in patients with LC-measurable disease), had a median time to progression from loss of CR of 4 months, highlighting the utility of sFLCs in early detection of relapse (Section 18.3.4).
20.4. HLC analysis at diagnosis

Figure 20.5. Progression-free and overall survival of patients achieving varying degrees of CR.

(A) Median time to progression of patients achieving sCR (n=109) is 50 months compared with 20 months and 19 months for groups attaining a CR (n=37) and near CR (nCR; n=91), respectively (p<0.001). (B) Those with sCR had a marked improvement in overall survival (median not-reached) compared with patients achieving CR (median 81 months) or nCR (median 60 months). (C) Median overall survival of patients with sustained sCR at 6 months from ASCT (n=75) was significantly longer than for those with a non-sustained sCR (n=34) (not reached vs. 5.5 years, respectively; p<0.001). [1] (Originally published by the American Society of Clinical Oncology).

Figure 20.6. Overall survival according to patterns of relapse or progression.

(A) Patients with a transformed pattern at relapse or progression had a significantly inferior overall survival to those who progressed with their original isoform (p<0.001). (B) In a subanalysis, patients with FLC escape and other transformed progression exhibited significantly inferior overall survival (p<0.05). [36] (Reproduced from [36] Copyright 2014, with permission from Elsevier).

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Figure 20.7. Kaplan-Meier curves of survival from first relapse according to patterns of relapse.

Median overall survival from relapse was 37.4 months, 23.5 months and 27.7 months for patients relapsing with intact immunoglobulin only, both intact immunoglobulin and FLCs, and FLC only (FLC escape), respectively (p=0.002). (This research was originally published in Blood © the American Society of Hematology).

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