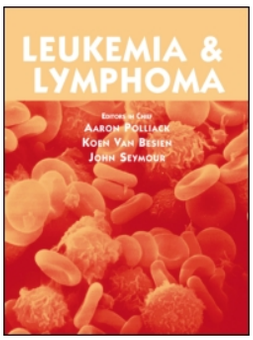

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ORIGINAL ARTICLE

Involved free light chain: an early independent predictor of response and progression in multiple myeloma

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ABSTRACT

Serum and urine protein electrophoresis (sPEP/uPEP) are the standard methods for monitoring of multiple myeloma (MM). However, a method of detection with shorter half-life, such as serum-free light chain (FLC), could detect the response or progression earlier. In total, 450 MM patients were assessed in first, second, and third line. Response and progression were classified according to International myeloma working group guidelines. The overall median time to partial response or better was detectable significantly earlier with involved free light chain (iFLC) 1.94 months (IQR: 1.61–2.23) compared to sPEP 5.39 months (IQR: 3.88–7.00). In first line, iFLC detected progression earlier compared to sPEP, particularly in patients with progression more than 18 months after best response. In conclusion, a response observed by iFLC occurs at least a median of 3 months before response is detected by sPEP/uPEP.

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KEYWORDS
Multiple myeloma; progression; response; serum-free light chain; m-protein

Introduction

Multiple myeloma (MM) is an incurable cancer. Beside treatment regimens, parameters evaluated at diagnosis such as b2-microglobulin (B2M), s-albumin, and high-risk chromosomal aberrations, are incorporated into risk stratification scores such as international staging system (ISS) and the revised ISS (R-ISS) [1,2]. During the last decades, there have been considerable advances in the treatment outcome of MM, making the response classification an important tool for prognostic evaluation. Overall, minimal residual disease (MRD) negativity is considered as a powerful predictor of favorable long-term outcomes in MM [3]. The duration of response has increased twofolds since the introduction of novel therapies. However, rapid progression can still be observed in patients with; high-risk cytogenetics, extramedullary disease, circulating plasma cells, or high ISS, and remains a challenge in patient management.

Traditionally, response and progression evaluation are carried out by M-protein measurements in serum and urine using protein electrophoresis (sPEP/uPEP). Serum-free light chain (sFLC) analysis is a complementary method in the initial diagnostic work-up as well as the assessment of complete response during follow-up. A possible advantage of sFLC measurement is the short serum half-life, 2–6 h, compared to immunoglobulins, up to 21 days [4,5], Thus, involved FLC (iFLC) analysis could, in a temporal fashion, be of higher value for earlier treatment evaluation and, thus enabling a potentially better clinical decision making. Therefore, we compared the impact of the iFLC analysis to sPEP/uPEP with regards to time to response (TTR) and progression.

Materials and methods

Study population

The study was approved by the Swedish Ethical Review Authority (EPM: 2017/349-31 and 2019-06564). The Karolinska University Laboratories, serving 20% of the total Swedish population, database was utilized in identifying patients with dysproteinaemia with evidence of MM. All individuals >18 years of age, who were referred to sFLC testing at Karolinska University Laboratory from 1 September 2009 until 1 September

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2017, were identified. Patients having an assay for sPEP and/or uPEP within 7 days of sFLC analysis were included in the cohort.

Results from electrophoresis, including M-protein isotype and size as well as results from sFLC were collected for all serum and urine samplings when both sPEP/uPEP and sFLC were available within 7 days. iFLC and sPEP are measured every fourth week, while uPEP is measured every 4th–12th weeks, according to local guidelines, in total data from 9001 timepoints where extracted. When available, hemoglobin (90.7%, $n = 8160$), creatinine (89.5%, $n = 8053$), eGFR (89.5%, $n = 8053$), calcium (87.0%, $n = 7830$), albumin (13.0%, $n = 1172$), and B2M (6.4%, $n = 575$) were also collected. Clinical data, including age, sex, diagnoses, and date of diagnoses was obtained from the medical journal. Serum FLC assays were conducted with latex-enhanced immunonephelometric assay (Siemens Healthcare GmbH, Erlangen, Germany). Total serum immunoglobulin (IgG, IgA, and IgM) concentrations were analyzed using immunoturbidimetric assay (Roche Diagnostics GmbH, Mannheim, Germany). Urine light chains (kappa and lambda) concentrations were analyzed using immunonephelometric assay (Siemens Healthcare GmbH, Erlangen, Germany). S/uPEP and immunofixation were performed with agarose gels on the Hydrasys/Hydrasys 2 platform (Sebia, Lisses, France). Fluorescent *in situ* hybridization (FISH) was performed as previously described [6] and grouped as high risk or low risk cytogenetic according to the international myeloma working group criteria [7].

Patients were grouped by measurable disease, defined by the diagnosis characteristics of sPEP/uPEP and iFLC, into four categories. Measurable by sPEP and iFLC (>1 g/dL M-protein in serum and iFLC > 10 mg/dL), measurable by sPEP only (>1 g/dL M-protein in serum and iFLC ≤ 10 mg/dL), measurable by uPEP and iFLC only (≤1 g/dL M-protein in serum and >200 mg/24 h M-protein in urine and iFLC > 10 mg/dL) and not measurable by sPEP/uPEP or iFLC (≤1 g/dL M-protein in serum and ≤200 mg/24 h M-protein in urine and iFLC ≤10 mg/dL). As only 26 patients did not have a measurable disease by either sPEP/uPEP and iFLC, this group was not assessed further.

In total, 1581 patients with MM were identified. To enable evaluation of response, patients with no additional measurement of iFLC and m-protein within 100 days of MM diagnosis were excluded. Patients that did not respond to first-line treatment or that had signs of progressive disease before response where also excluded.

Statistical analyses

The primary endpoints were the TTR and the time to progression (TTP), measured by iFLC and sPEP/uPEP, regardless of line of treatment. TTR was calculated as time from the first sampling date at diagnosis until date of at least partial remission (PR), according to the definition by the International myeloma working group (IMWG) response criteria for sPEP and uPEP [8]. For iFLC, partial response was defined as a reduction of iFLC of ≥50%, regardless of whether the M-protein was measurable by sPEP/uPEP or not.

TTP was defined as the time from the best response, until progression as defined by IMWG for sPEP and uPEP [8]. For iFLC, progression was defined as an increase of iFLC ≥25% and an absolute increase of ≥100 mg/L, regardless of whether the M-protein was measurable by sPEP/uPEP.

The secondary endpoints were TTR and TTP for the first, second, third response/progression, measured by iFLC and sPEP/uPEP. The TTR and TTP are presented at the median and 95% confidence interval.

Univariate Cox regression was performed to estimate the effect of prognostic factors with hazard ratios (CI threshold: 95% and p value threshold <0.05) reported. Kaplan–Meier method and Log-rank tests were performed for group comparisons.

Results

The patient's characteristics are presented in Table 1. The median age was 68 years, with 262 (58%) being male. Cytogenetics was evaluated in 209 patients at diagnosis, of these 120 were high risk according to IMWG classification [7]. The number of patients that were comparatively assessed for the first, the second, and the third responses were 450/450/390, 129/129/78, and 30/30/15, for iFLC, sPEP, and uPEP, respectively. For progression, the consecutive comparable values for the first, the second, and the third progression were 302/302/182, 53/53/34, and 15/15/8, for iFLC, sPEP, and uPEP, respectively.

TTR

For the responses in the first line treatment, the median TTR was detectable significantly earlier with iFLC (2.20 months) compared to sPEP (5.60 months) and uPEP (19.2 months), $p < 0.001$ in both cases. The corresponding numbers for the median TTR in all responses were iFLC (1.94 months) compared to sPEP (5.39 months) and uPEP (13.3 months), $p < 0.001$ for both comparisons. The TTR was subsequently assessed

by heavy chain subtype. The median TTR in first line of treatment was significantly shorter for iFLC (1.7 months, 95% CI: 1.4–2.1) compared to sPEP (2.3 months, 95% CI: 2.0–2.6) in patients with IgG subtype, $p = 0.007$ (Figure 1(A)). No significant difference was observed in IgA subtype, 2.0 and 2.4 months (95% CI: 1.4–2.6 and 1.6–3.2) for iFLC and sPEP, respectively, $p = 0.14$ (Figure 1(B)). No significant differences in TTR-between subtypes were observed in second or third-line response.

Table 1. Patient characteristics.

	No. of patients (%)
Gender, male no. (%)	262 (58)
Age, years median (IQR)	68 (61–75)
	Median (IQR)
Hemoglobin, g/L	111 (98–124)
Creatinine, µmol/L	87 (67–122)
eGFR, mL/min/1,73 m^2	65 (43–78)
Calcium, mmol/L	2.3 (2.2–2.4)
β-2-microglobulin,	3.56 (251–3.56)
Albumin	32 (29–36)
Serum M-spike g/dL	1.8 (0.2–3.5)
Urine M-spike, mg/L	29 (4–321)
Involved FLC, mg/L	149 (36–686)
	No. patients (%)
Abnormal FLC ratio	426 (95)
Heavy chain	
IgG	273 (60.9)
IgA	89 (19.9)
IgM and other	6 (1.3)
Light chain only	78 (17.4)
Light chain	
Kappa	273 (60.9)
Lambda	175 (39.1)
Cytogenetics	
High risk	120 (57.4)
t(4;14)	11 (5.2)
t(14;16)	4 (1.9)
t(14;20)	0 (0)
Gain(1q)	65 (31.1)
Del (17p)	22 (10.5)
Non-hyperdiploidy	65 (31.1)
Standard risk	89 (42.6)
ISS	
I + II	240 (57.4)
III	104 (42.6)

Median and interquartile ranges or number and percentages for the different parameters are presented. High risk cytogenetic defined as presence of t(4;14), t(14;16), t(14;49), gain1q, del17/17p, and/or nonhyperdiploidy.
IQR: interquartile range; eGRF: estimated glomerular filtration rate; FLC: free light chain; ISS: International Staging System.

An earlier detection of response by iFLC compared to uPEP were observed in first and second line of treatment. No differences were observed in the third line of treatment, which most probably was due to the sample size, where only 15 patients could be evaluated with uPEP. The median and IQR TTR for the first, second, third and all responses, regardless of subtype, are presented in Table 2.

We further investigated the TTR by measurable disease groups. Patients without a response within the first year after MM diagnosis were excluded. No significant difference in TTR was observed between sPEP and iFLC in the group of measurable disease in sPEP only ($p = 0.46$), i.e. patients with iFLC $\leq$ 10 mg/dL (Figure 2(A); Table 3). In the group with measurable disease by both sPEP and iFLC, the response was observed significantly earlier by iFLC compared to sPEP, median TTR 1.8 months (95% CI: 1.4–2.2) and 2.3 months (95% CI: 1.9–2.7), respectively, $p = 0.04$ (Figure 2(B); Table 3). In patients with measurable disease by uPEP and iFLC, response was detected earlier by iFLC (median TTP 1.4 months) compared to uPEP (median TTP 1.9 months), $p = 0.003$ (Figure 2(C)).

In second line of response, no significant difference was observed between iFLC and sPEP in patient with measurable disease by sPEP and iFLC of either >10 mg/dL or ≤10 mg/dL, Supplementary Table 1a. Only 30 patients were available for evaluation of third line of response, hence no further analysis by measurable disease were performed.

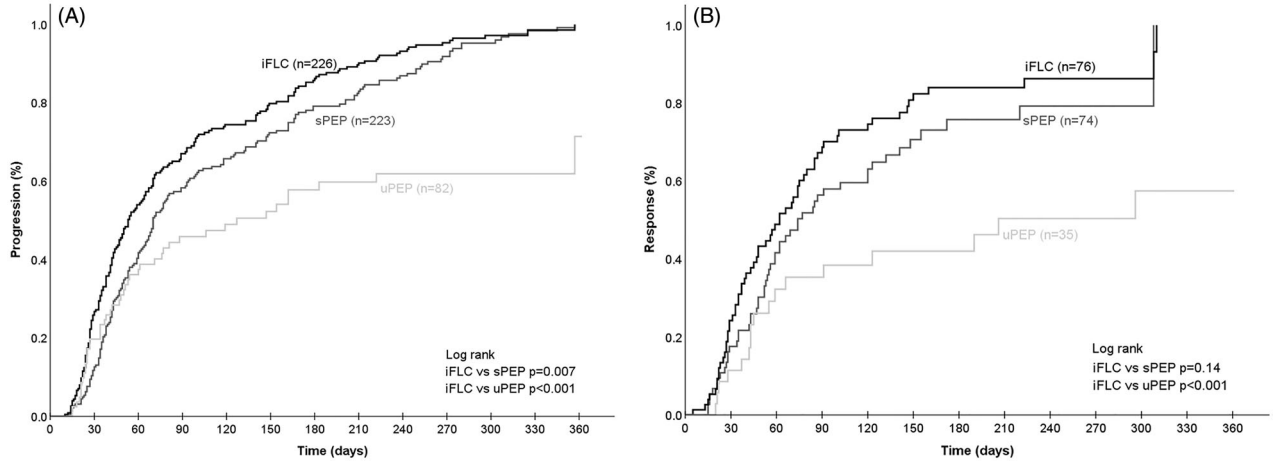

Figure 1. Kaplan–Meier plots of the time to response in first line of treatment measured by involved free light chain (iFLC), serum protein electrophoresis (sPEP) and urine electrophoresis (uPEP). (A) Patients with IgG subtype. (B) Patients with IgA subtype.

Table 2. Time to response (TTR), in months, in the 1st, 2nd, 3rd line of treatment and on all occasions of responses (in all 3 lines).

	n	Median	IQR	*p*-value
TTR first line				
iFLC	450	2.2	1.2–6.9	
sPEP	450	5.6	1.7–17.7	<0.001
uPEP	390	19.2	3.7–43.9	<0.001
TTR second line				
iFLC	129	1.1	0.5–3.3	
sPEP	129	5.4	0.7–12.9	<0.001
uPEP	78	4.7	0.9–11.7	0.002
TTR third line				
iFLC	30	0.9	0.6–1.4	
sPEP	30	4.8	1.6–18.3	<0.001
uPEP	15	1.3	0.8–7.6	0.13
TTR regardless of line				
iFLC	609	1.9	0.1–6.2	
sPEP	609	5.4	1.6–16.5	<0.001
uPEP	483	13.3	2.9–39.7	<0.001

The median and interquartile ranges (IQR) are presented for the time to response (TTR) in the first, second, third and on all occasions of responses (in all three lines).
iFLC: involved free light chain; sPEP: serum protein electrophoresis; uPEP: urine protein electrophoresis.

Table 3. Time to response, in months, in the first line of treatment grouped by measurable disease.

	n	Median	95% CI	*p*-value
sPEP and iFLC				
iFLC	181	1.8	1.4–2.2	
sPEP	182	2.2	1.9–2.7	0.04
uPEP	69	3.9	1.7–6.1	<0.001
sPEP only				
iFLC	79	2.2	1.7–2.7	
sPEP	80	2.3	1.9–2.9	0.46
uPEP	21	NR	NR	0.002
uPEP and iFLC				
iFLC	97	1.4	1.2–1.6	
sPEP	49	NR	NR	<0.001
uPEP	87	1.9	1.5–2.3	0.003

sPEP and FLC was defined as >1 g/dL M-protein in serum and iFLC > 10 mg/dL, sPEP only as >1 g/dL M-protein in serum and iFLC ≤ 10 mg/dL, uPEP and iFLC as ≤1 g/dL M-protein in serum and > 200 mg/24 h M-protein in urine and iFLC > 10 mg/dL).
iFLC: involved free light chain; sPEP: serum protein electrophoresis; uPEP: urine protein electrophoresis; NR: not reached.

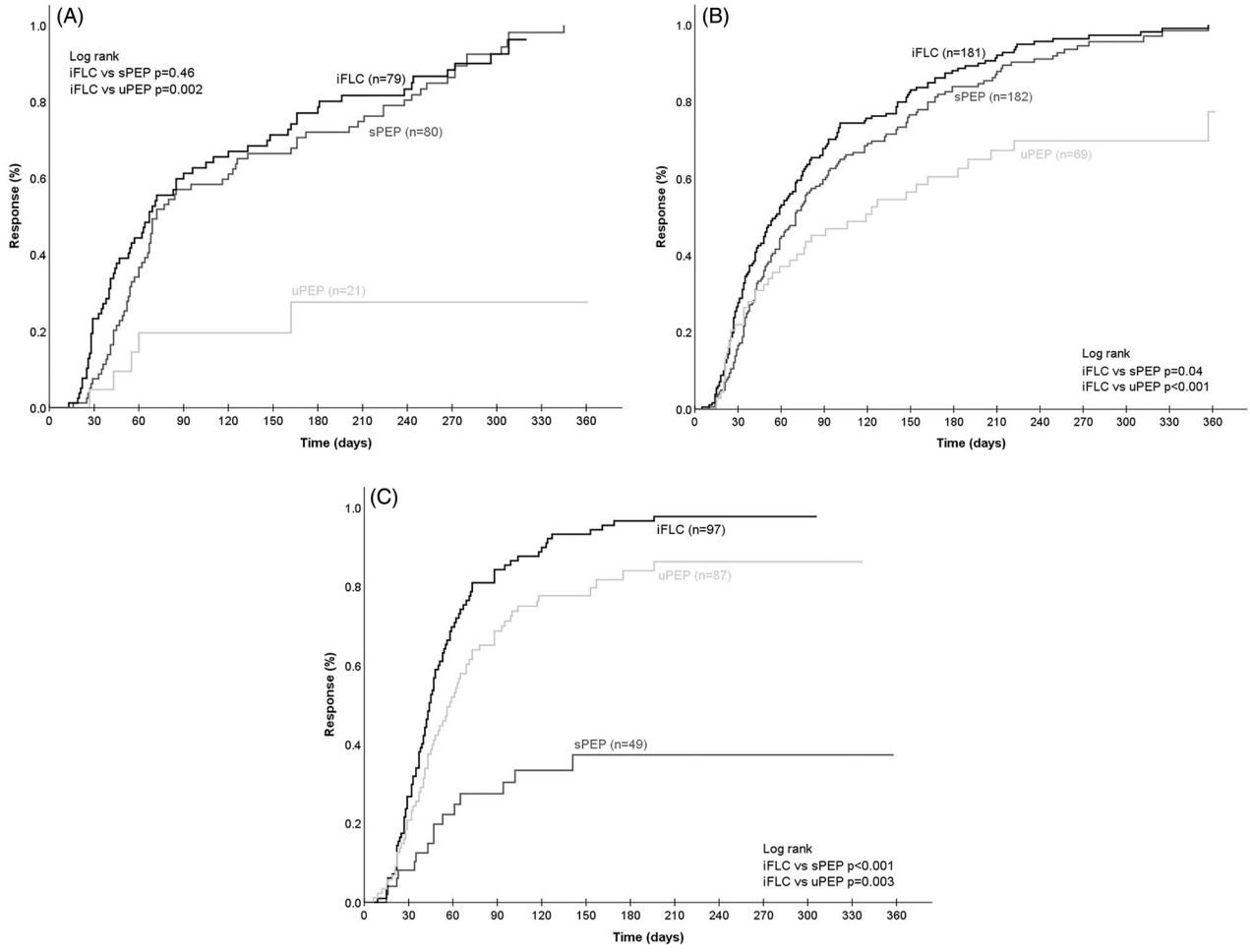

Figure 2. Time to first response measured by involved free light chain (iFLC), serum protein electrophoresis (sPEP) and urine electrophoresis (uPEP). (A) Measurable disease by sPEP only, i.e. >1 g/dl M-protein in serum and iFLC ≤ 10 mg/dl. (B) Measurable disease by sPEP and iFLC, i.e. >1 g/dl M-protein in serum and iFLC > 10 mg/dl. (C) Measurable disease by iFLC and uPEP only, ≤1 g/dl M-protein in serum and >200 mg/24 h M-protein in urine, and iFLC > 10 mg/dl).

Table 4. Time to progression (TTP), in months, in the first, second, thirdof treatment and on all occasions of responses (in all three lines).

	n	Median	IQR	*p*-value
TTP first line				
iFLC	302	18.9	8.2–35.1	
sPEP	302	18.9	7.5–24.6	0.27
uPEP	182	31.4	15.0–47.6	<0.001
TTP second line				
iFLC	53	9.9	1.5–21.9	
sPEP	53	11.3	1.9–24.5	0.13
uPEP	34	21.2	9.2–32.6	0.02
TTP third line				
iFLC	15	3.6	1.1–16.0	
sPEP	15	1.8	0.9–15.8	0.95
uPEP	8	19.4	8.8–40.7	0.122
TTP regardless of line				
iFLC	370	16.6	5.8–33.0	
sPEP	370	16.7	5.3–34.8	0.098
uPEP	224	29.8	14.1–45.5	<0.001

The median and interquartile ranges are presented median and 95% confidence interval (CI) for the time to progression (TTP) in the first, second, third, and on all occasions of progression (in all three lines).
iFLC: involved free light chain; sPEP: serum protein electrophoresis; uPEP: urine protein electrophoresis.

TTP

In first progression, the median TTP was detectable at the same time with iFLC compared to sPEP, 18.9 and 18.8 months, respectively. When evaluating all progression occasions, no significant difference in median TTP between iFLC (16.6 months) and sPEP (16.7 months) were observed. The differences between iFLC and uPEP in all measurements were significant except the third line, in which only eight patients were available for the uPEP analyses. The median and IQR of TTP for the first, second, third, and all progressions are presented in Table 4. No differences in TTP by heavy chain type was observed in either first or second line of progression. Third line of progression was not assessed due to the low number of patients in this group.

Thereafter, TTP was assessed by measurable disease groups. Similar to the results in the complete cohort, no significant difference in TTP were observed in 1st progression in the group with measurable disease by sPEP and iFLC (Figure 3(A); Table 5). In contrast, in

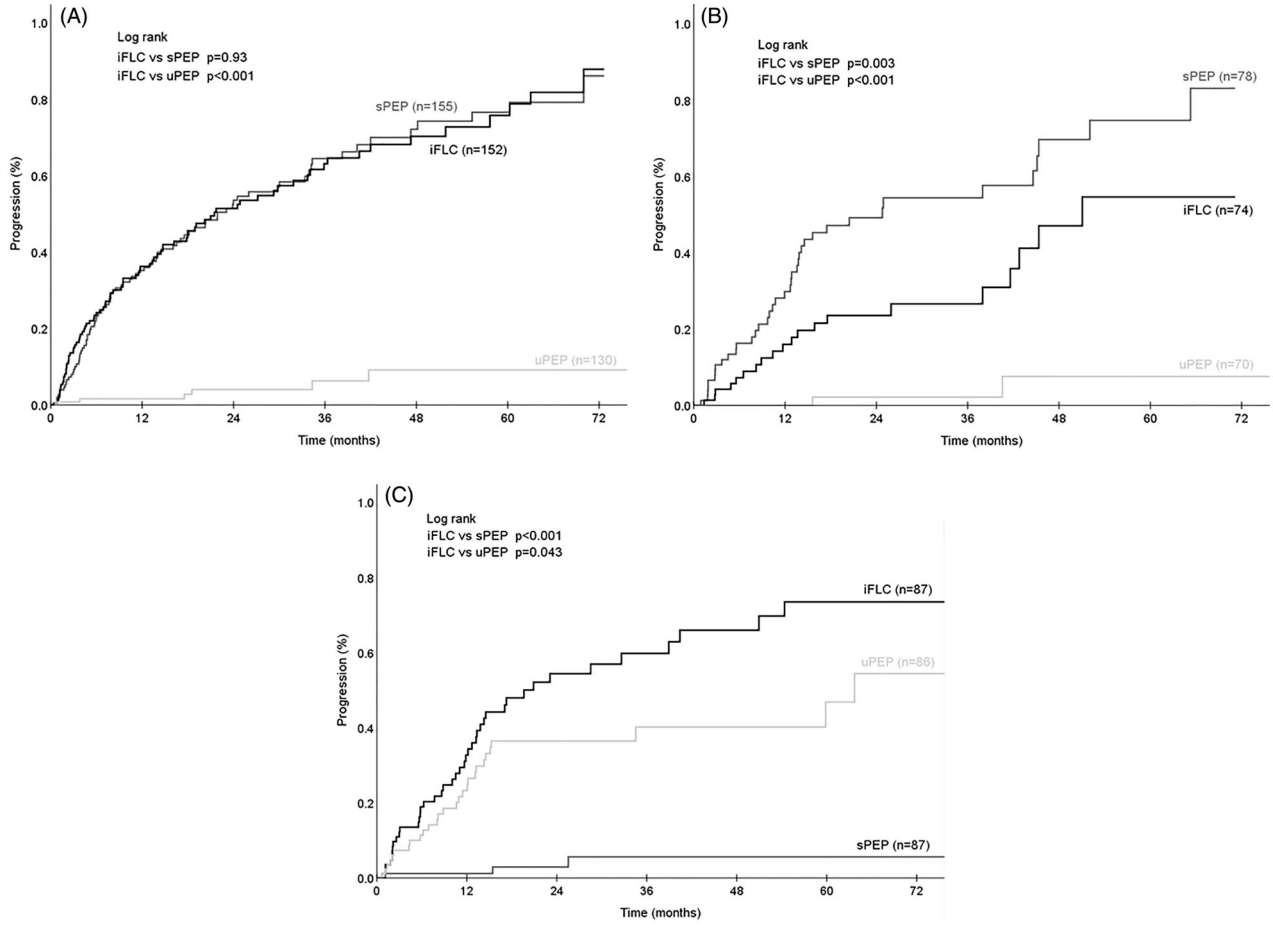

Figure 3. Time to first progression measured by involved free light chain (iFLC), serum protein electrophoresis (sPEP) and urine electrophoresis (uPEP). (A) Measurable disease by sPEP and iFLC, i.e. >1 g/dl M-protein in serum and iFLC > 10 mg/dl. (B) Measurable disease by sPEP only, i.e. >1 g/dl M-protein in serum and iFLC ≤ 10 mg/dl. (C) Measurable disease by iFLC and uPEP only, ≤1 g/dl M-protein in serum and >200 mg/24 h M-protein in urine, and iFLC > 10 mg/dl).

Table 5. Time to first-line progression, in months, grouped by measurable disease.

	n	Median	95% CI	p-value
sPEP and iFLC				
iFLC	152	21.8	15.3–28.45	
sPEP	155	21.5	7.5–24.6	0.93
uPEP	130	NR	NR	<0.001
sPEP only				
iFLC	74	24.8	3.3–46.3	
sPEP	78	51.1		0.003
uPEP	70	NR	NR	<0.001
uPEP and iFLC				
iFLC	87	19.6	6.0–33.2	
sPEP	87	NR	NR	<0.001
uPEP	86	63.7	–	0.04

sPEP and FLC was defined as >1 g/dL M-protein in serum and iFLC > 10 mg/dL, sPEP only as >1 g/dL M-protein in serum and iFLC ≤ 10 mg/dL, uPEP and iFLC as ≤1 g/dL M-protein in serum and > 200 mg/24 h M-protein in urine and iFLC > 10 mg/dL).
iFLC: involved free light chain; sPEP: serum protein electrophoresis; uPEP: urine protein electrophoresis; NR: not reached.

patients with measurable disease by sPEP only, the progression was observed significantly earlier with sPEP compared to iFLC (median TTP 24.8 and 51.1 months, respectively), $p = 0.003$ (Figure 3(B)). iFLC detected a progression significantly earlier (19.6 months) compared to uPEP (63.7 months) in the group with measurable disease in uPEP and iFLC, $p < 0.001$ (Figure 3(C)). In second progression, no differences in TTP were observed between iFLC and sPEP in patients with measurable disease by sPEP and iFLC, $p = 0.56$, nor in patients with measurable disease by sPEP only, $p = 0.63$.

Sub-analysis of the TTP in late and early progression

We further grouped the population as either early (progression occurring within the first 18 months) or late progressors (progression occurring after 18 months). In late progressors, regardless of line of progression, detection of progression occurred significantly earlier with iFLC (34.1 months, range 29.3–38.0) compared to sPEP (36.0 months, range 32.2–40.4), $p = 0.03$, and uPEP (38.4 months, range 34.4–45.5), $p = 0.04$. In first TTP, late progressors also exhibited shorter median TTP when evaluated by iFLC compared to uPEP, 35.0 and 38.9 months, respectively ($p = 0.04$), while no significant difference was observed between iFLC and sPEP, 36.4 months ($p = 0.07$) (Supplementary Figure 1(A,B)).

Sub analysis of changes in renal function at time of progression in patients relapsing with increases of iFLC

Patients relapsing with an iFLC increase was 168 in first-line progression, 49 in second-line progression and 11 in third-line response. To evaluate changes in renal function at the time of progression, only patients with measurements of both iFLC and creatinine at both the time of best response and the time of progression (delta iFLC and delta creatine) were included in this subanalysis. There was no correlation of delta iFLC and delta creatinine in patients regardless of line of progression. $R^2 = 0.009$ (Supplementary Figure 4(A)). Patients were further grouped by increase or no increase of creatinine at the time of progression. The increase of creatinine was defined as an elevation from the time of the best response to the time of progression by > reference change value for creatinine. No correlation was observed for delta iFLC and delta creatinine in either group, $R^2 < 0.001$ and $R^2 = 0.002$, for patients with and without creatinine increase, respectively (Supplementary Figure 4(B,C)).

Discussion

The combination of iFLC and sPEP has repetitively demonstrated high sensitivity in the diagnoses of MM [9]. Furthermore, IMWG guidelines recommend assessment of iFLC when screening for plasma cell dyscrasias [10]. IMWG also includes sFLC in MM response criteria, but only in assigning stringent complete response, sFLC ratio, or in patients where serum and urine M-protein is not detectable [8]. The higher sensitivity of iFLC compared to uPEP with IFE have led to suggestions that monitoring should be carried out with iFLC together with sPEP [9]. Since sFLC serum dynamics are more rapid due to a significantly shorter half-life compared to immunoglobulins, an earlier prediction of response (including progression) would be anticipated. Thus, we designed this study to assess the differences in time to detection of response and progression by iFLC compared to sPEP and uPEP.

To our knowledge, this is the largest cohort, with a median follow-up time of 4 years, with consecutive simultaneous measurement of iFLC and sPEP/uPEP. The large number of observations available for this real-world cohort enabled a temporal evaluation of iFLC to sPEP/uPEP. The most important clinically relevant finding in our study was that response was detected significantly earlier with iFLC (1.94 months), as measured with $a \geq 50\%$ reduction (PR), compared to sPEP (5.39 months) and uPEP (13.3 months).

Earlier response by iFLC have been indicated as a superior factor in prediction of overall response [11–13]. For this study, the response classification of iFLC of >50% reduction of iFLC was applied regardless if patients had measurable disease by sPEP and/or

uPEP. We observed that iFLC detected response earlier compared to uPEP in patients with measurable disease in iFLC and uPEP. These findings support previous results that iFLC provides a superior detection sensitivity compared to the uPEP when monitoring response in MM patients [9]. While an earlier response with iFLC compared to uPEP also was seen in patients with measurable disease in sPEP, uPEP were infrequently assessed in these patients. Consequently, the earlier detection of response by iFLC compared to uPEP observed in these groups should be interpreted with caution.

The monitoring of response by iFLC is not recommended when assessing patients with measurable disease in serum or urine, i.e. >1 g/dL serum M-protein and/or >200 mg/24 h in urine M-protein [8]. Thus, the classification of response, when M-protein is measurable, as assessed by sPEP and uPEP is well established, while iFLC is not yet a consensus method for this purpose [8,12]. Our findings indicated that iFLC assessment can detect response, in first-line of treatment, earlier in patients with a measurable disease by sPEP when the iFLC was >10 mg/dL at diagnose. Interestingly, there was no difference in median TTR by iFLC and sPEP in patients with measurable disease by sPEP and iFLC ≤ 10 mg/L. We therefore suggest that monitoring of response by iFLC should be performed also in patients with measurable disease in sPEP and uPEP.

The half-life of IgG is in part dependent on the plasma concentration due to saturation of the neonatal FC receptor which affects the IgG recycling [14]. Thus, response evaluation in patients with IgG M-protein may be affected by the recirculating IgG. As iFLC is not affected by this recycling an earlier detection of response, when assessed by iFLC, could be anticipated in IgG myeloma. In line with this, the median TTR by iFLC assessment was significantly shorter compared to sPEP assessment in patients with IgG myeloma. By contrast, in patients with IgA subtype, no difference in TTR could be seen between iFLC and sPEP. These findings support that monitoring of response by iFLC could be performed in patients with both IgG and IgA myeloma.

In the Myeloma IX study, relapsed patients that had FLC escape, defined as an increase in FLC value (≥25% increase and an absolute increase of ≥100 mg/L without a concurrent increase in M-protein), had approximately 12-month shorter overall survival compared to patients relapsing with detectable M-protein [15]. A serial sFLC evaluation could enable earlier prediction of biochemical as well as of clinical relapse [16,17]. In line with these results, we could also demonstrate an earlier detection of progression in patients with a late progression in first line. We could also demonstrate a difference in TTP in the 2nd line. Interestingly, in patients with an M-protein >1 g/dL and iFLC >10 mg/dL, the detection of progression appears to occur at the same time, implying that monitoring in these patients could be performed with iFLC. However, as an earlier detection progression by sPEP could be observed in patients with an iFLC ≤10 mg/dL, sPEP cannot be omitted when monitoring patients during the follow-up. In conclusion, iFLC may also be useful as monitoring tool in predicting relapse.

One of the major challenges, when evaluating difference in temporal changes in sPEP and iFLC, is that while 90–95% of MM patients with intact M-protein will have abnormal sFLC ratio and elevated iFLC, patients can present with m-protein detectable by sPEP only [18]. Moreover, local guidelines recommend monitoring of uPEP everyone to 3 months, which inherently, impacts the later detection of response and progression by uPEP compared to both iFLC and sPEP.

In conclusion, $a \geq 50\%$ decrease in iFLC, i.e. PR or better, predicted responses at least 3 months before sPEP (median), regardless of the line of the treatment. The early detection of response might benefit the patients through a dose reduction and/or limit the number of drugs used in combination, due to eventual side effects. Capturing a 25% increase, with an absolute increase of ≥100 mg/L in iFLC, should be a marker of progression in MM patients. This might lead to a better monitoring of the patients and, in some cases, an earlier start of the treatment and hopefully preventing end organ damage in a relapse setting. The sFLC assay is consequently a valuable tool for predicting the response to treatment as well as the risk of progression and should be included when monitoring of patients with MM.

Authors' contributions

Conceptualization, H.N.; methodology, H.N., C.G., J.L., and A.V.; formal analysis, J.L., C.G. and A.V.; resources, C.G, G.A., and H.N.; data curation, C.G, J.L., and A.V.; writing – original draft preparation, H.N. and C.G.; writing – review and editing, all authors; supervision, H.N.; project administration, H.N.; funding acquisition, H.N. All authors have read and agreed to the published version of the manuscript.

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