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LETTER TO THE EDITOR

Urine immunofixation negativity is not necessary for complete response in intact immunoglobulin multiple myeloma: Retrospective real-world confirmation

To the Editor,

The definition of complete disease response (CR) in multiple myeloma (MM) continues to be reevaluated. The last widely accepted model of response assessment was proposed by the International Myeloma Working Group (IMWG) in 2016.[1] Urine immunofixation (uIFE), one of the CR parameters, is being frequently omitted from CR evaluation in routine clinical practice. Patients with missing uIFE are then reported as having very good partial response (VGPR).[2] It has been recently suggested in retrospective analysis by Lahuerta et al[3] that patients with intact immunoglobulin myeloma (IIMM) who lack uIFE examination present with the very same prognosis as the patients with negative uIFE and therefore uIFE might not be necessary for CR definition in such patients.

Our analysis of potential benefit of uIFE was aimed on patients with IIMM. Light-chain-only MM patients were excluded. We aimed at the robust analysis of real-world outcomes based on data collected by the Czech Registry of Monoclonal Gammopathies (RMG: https://rmg.healthregistry.org/) to compare the outcomes of patients with IIMM reaching CR and comparison of their outcomes regarding the availability of uIFE at the time of response assessment. Patients from Czech centers in RMG registry (from 2007 to 2019) with IIMM-treated front line with immunomodulatory drugs and/or proteasome inhibitors were selected. All patients signed the informed consent forms upon entering the RMG. The treatment response and time-to-event endpoints were evaluated. Progression free survival (PFS) was defined as time from start of the treatment to disease progression or death (regardless of cause of death), whichever comes first. Time to progression (TTP) was defined as time from start of treatment to disease progression, with deaths from causes other than progression censored. Overall survival (OS) was defined as time from diagnosis to death.[4] Diagnosis of MM was based on IMWG criteria.[4]

For the purpose of this particular analysis, IIMM patients were divided into four groups based on the result of IFE after final response to treatment (Figure S1). The first group comprised of 301 patients with both serum (sIFE) and uIFE negative (CR), the second group 180 patients with serum immunofixation negative and uIFE not available (uncertain CR; uCR). These are the patients who would otherwise be marked as VGPR but were transferred from this group to uCR group to perform the analysis. The third group consisted of 16 patients with sIFE negative and uIFE positive. The fourth group defined as VGPR group contains 654 patients, that is, those with positive sIFE or intact immunoglobulin drop >90% regardless of uIFE availability, without patients with uIFE not available transferred to uCR group. Since we focused on the importance of IFE, impact of bone marrow plasma cells on survival parameters was not calculated.

Overall, 43.2% (497/1151) patients had negative sIFE. 26.2% (301/1151) had negative uIFE (CR group), 15.6% (180/1151) had uIFE not available (uCR group), and 1.4% (16/1151) had uIFE positive and sIFE negative. 56.8% of patients were evaluated as having VGPR (654/1151). Only 16 patients were identified as sIFE negative and uIFE positive. Statistically significant differences between groups include age (VGPR patients 66 years and CR 64 years), ISS stage (ISS III in 24.9% in CR group, 33.3% in uCR group, and 35.2% in VGPR group), and cytogenetic risk (high in 27.7% in CR group, 53.1% in uCR group, and 34.8% in VGPR group). Details are shown in Table 1.

The PFS of patients with CR and uCR was comparable and was better than PFS in VGPR group. Median PFS was 39.7 months (95th CI: 33.2-46.2) in CR group, 36.2 months (95th CI: 32.1-40.2) in uCR, and 25.5 months (23.9-27.1) in VGPR group (Figure 1). Median OS was 91.9 months (95th CI: 70.4-113.4) in CR group, 79.0 months (95th CI: 56.4-101.6) in uCR and 64.0 months (54.2-68.9) in VGPR group. Median TTP was 44.6 months (95th CI: 37.1-52.0) in CR group, 37.4 months (95th CI: 31.9-42.8) in uCR group, and 26.4 months (24.8-28.0) in VGPR group. The differences between CR and uCR groups versus VGPR group were statistically significant in PFS, OS, and TTP (all $P < .001$) but there was no statistical difference between CR and uCR group (see Figure 1). Time-to-event intervals were not different when compared CR, uCR group and group of 16 patients with positive uIFE and negative sIFE (PFS $P = .106$, TTP $P = .130$ and OS $P = .10$).

This is to our knowledge the first report of real-world patients treated under common clinical conditions and providing not only PFS but also OS data in patients with MM in CR comparing the outcomes of patients with uIFE negative and uIFE not available. There is only one report on a similar topic by Lahuerta et al dealing with patients who participated in the clinical trial.[3] Lahuerta et al showed no differences in PFS among patients with CR and uCR and lower PFS in VGPR patients compared to uCR patients at 2 years. The same results are shown in our study with no PFS difference among groups with CR and uCR and a significant difference compared to VGPR. Lahuerta et al also identified only 3 patients (1.8%) in whom uIFE was positive when sIFE was negative.

TABLE 1 Baseline patient´s characteristics

Characteristics at initiation of 1st line therapya	Immunofixation after treatment					Serum negative & urine positive
	CR group	uCR group	Pb	VGPR group	Pc	
Sex	n = 301	n = 180		N = 654		n = 16
Man	169 (56.1%)	91 (50.6%)	.234	365 (55.8%)	0.414	12 (75.0%)
Woman	132 (43.9%)	89 (49.4%)		289 (44.2%)		4 (25.0%)
Age	n = 301	n = 180		N = 654		n = 16
≤50	26 (8.6%)	12 (6.7%)	.728	43 (6.6%)	**.006**	0 (0.0%)
51-65	152 (50.5%)	94 (52.2%)		270 (41.3%)		8 (50.0%)
>65	123 (40.9%)	74 (41.1%)		341 (52.1%)		8 (50.0%)
Median (min–max)	64 (26-91)	64 (29-85)	.616	66 (33-87)	**<.001**	66 (54-82)
Follow-up (mo)	n = 301	n = 180		N = 654		n = 16
Median (min–max)	43.6 (4.2-139.9)	38.0 (1.2-124.8)	**.018**	35.7 (0.4-155.7)	**<.001**	40.8 (6.3-103.4)
M-protein serum (g/l)	n = 301	n = 180		N = 649		n = 16
Median (min–max)	26.0 (0.0-85.7)	22.4 (0.0-89.0)	.406	35.0 (0.0-108.9)	**<.001**	6.2 (0.0-43.0)
M-protein type	n = 301	n = 180		N = 654		n = 16
IgG	196 (65.1%)	110 (61.1%)	.263	449 (68.7%)	.196	8 (50.0%)
IgA	98 (32.6%)	61 (33.9%)		189 (28.9%)		6 (37.5%)
Biclonal, IgD or IgM	7 (2.3%)	9 (5.0%)		16 (2.4%)		2 (12.5%)
Light chain type	n = 301	n = 180		N = 654		n = 16
Kappa	160 (56.5%)	101 (56.1%)	.566	395 (60.4%)	.225	10 (62.5%)
Lambda	128 (42.5%)	75 (41.7%)		256 (39.1%)		5 (31.3%)
Biclonal	3 (1.0%)	4 (2.2%)		3 (0.5%)		1 (6.3%)
ISS	n = 281	n = 168		N = 579		n = 15
Stage 1	106 (37.7%)	54 (32.1%)	.152	152 (26.3%)	**.004**	5 (33.3%)
Stage 2	105 (37.4%)	58 (34.5%)		223 (38.5%)		4 (26.7%)
Stage 3	70 (24.9%)	56 (33.3%)		204 (35.2%)		6 (40.0%)
ECOG PS	n = 284	n = 162		N = 589		n = 15
0	57 (20.1%)	33 (19.2%)	.120	81 (13.8%)	**.026**	1 (6.7%)
1	159 (56.0%)	88 (51.2%)		355 (60.3%)		11 (73.3%)
2	54 (19.0%)	32 (18.6%)		101 (16.1%)		3 (20.0%)
3-4	14 (4.9%)	19 (11.0%)		52 (8.8%)		0 (0.0%)
Cytogenetic risk[d]	n = 94	n = 49		N = 204		n = 5
Standard risk	68 (72.3%)	23 (46.9%)	**.003**	133 (65.2%)	**.011**	4 (80.0%)
High risk	26 (27.7%)	26 (53.1%)		71 (34.8%)		1 (20.0%)
Osteolytic lesions[e]	n = 283	n = 160		N = 593		n = 15
Negative	45 (15.9%)	33 (19.4%)	.490	108 (18.2%)	.740	2 (13.3%)
1-2 lesions	50 (16.7%)	24 (14.1%)		86 (14.5%)		1 (6.7%)
More than 2 lesions	167 (62.5%)	109 (64.1%)		383 (64.6%)		12 (80.0%)
Accelerated osteoporosis	11 (3.9%)	4 (2.4%)		16 (2.7%)		0 (0.0%)
Extramedullary mass	n = 287	n = 161		N = 599		n = 15
No	247 (86.1%)	149 (87.1%)	.745	545 (91.0%)	.064	12 (80.0%)
Yes	40 (13.9%)	22 (12.9%)		54 (9.0%)		3 (20.0%)

Note: Statistical significance determined using ML chi-square test in case of categorical variables and Kruskal-Wallis test in case of continuous variables. Statistically significant differences are shown in bold.

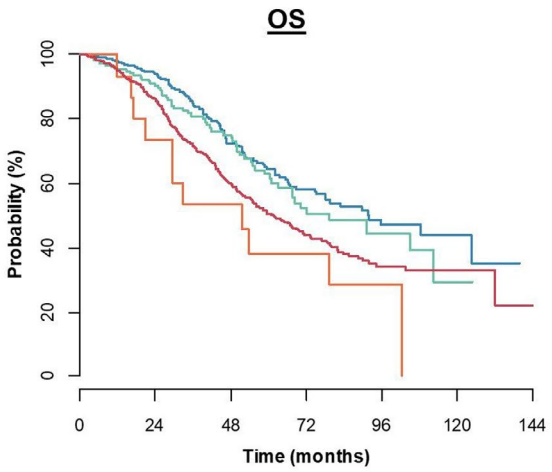
[a]N (%) in case of categorical variables, median (minimum-maximum) in case of continuous variables.

[b]Patients with negative and unknown immunofixation in urine compared.

[c]Patients with negative, unknown immunofixation in urine and VGPR compared.

[d]High risk defined as presence of t(4;14), t(14;16) or del(16p13); samples collected at time of MM diagnosis.

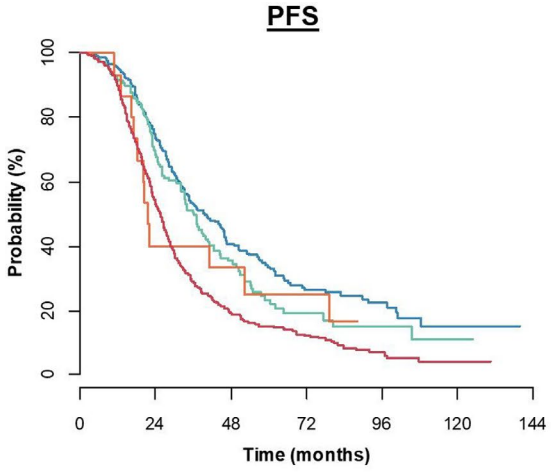
[e]The most positive result from: X-ray, MRI, CT, PET/CT, and LDCT reported.



p<0.001
p=0.314

OS, Complete molecule	CR group	uCR group	VGPR group	Serum negative & urine positive
N events[1]	301/96	180/57	654/269	16/11
Median (95% CI)	91.9 (70.4–113.4)	79.0 (56.4–101.6)	61.5 (54.2–68.9)	51.6 (23.2–80.1)
Probability of survival without event, % (95% CI)				
12 months	98.0 (95.6–99.1)	95.4 (91.0–97.7)	95.1 (93.1–96.6)	93.3 (61.3–99.0)
24 months	94.0 (90.4–96.2)	90.2 (84.5–93.9)	86.2 (83.1–88.7)	73.3 (43.6–89.1)
36 months	84.5 (79.4–88.5)	80.8 (73.3–86.4)	71.6 (67.5–75.2)	53.3 (26.3–74.4)
48 months	72.3 (65.8–77.8)	75.1 (66.7–81.7)	59.9 (55.2–64.2)	53.3 (26.3–74.4)
60 months	64.4 (57.3–70.7)	62.8 (52.9–71.2)	50.6 (45.7–55.3)	38.1 (14.6–61.6)

[1]Event defined as occurrence of death.



p<0.001
p=0.100

PFS, Complete molecule	CR group	uCR group	VGPR group	Serum negative & urine positive
N events[1]	301/172	180/106	654/458	16/12
Median (95% CI)	39.7 (33.2–46.2)	36.2 (32.1–40.2)	25.5 (23.9–27.1)	21.6 (19.5–23.8)
Probability of survival without event, % (95% CI)				
12 months	95.5 (92.4–97.4)	91.9 (86.6–95.1)	90.0 (87.3–92.1)	93.3 (61.3–99.0)
24 months	73.5 (67.8–78.4)	68.3 (60.3–75.0)	53.2 (49.0–57.2)	40.0 (16.5–62.8)
36 months	53.1 (46.7–59.2)	50.5 (41.9–58.4)	29.1 (25.2–33.1)	40.0 (16.5–62.8)
48 months	40.7 (34.2–47.2)	35.4 (27.0–43.9)	19.2 (15.7–23.0)	33.3 (12.2–56.4)
60 months	33.5 (27.0–40.1)	23.2 (15.6–31.6)	15.1 (11.7–18.8)	25.0 (6.9–48.8)

[1]Event defined as occurrence of progression or death.

FIGURE 1 PFS and OS according to result of immunofixation and final response to treatment

Our study shows similar results showing only 16 such patients (3.8% of all sIFE negative patients and 0.5% of all patients with IIMM). On the top of the findings, Lahuerta et al also showed the same MRD negativity (defined as flowcytometric negativity in the bone marrow) in CR and uCR patients (76% in CR and 75% in uCR) which supports the unnecessity of uIFE.[3]

These observations are obviously limited to patients with IIMM. Another weakness of the study is its retrospective nature with all the limitations, such as impossibility to calculate the sample size and power in advance. The strengths of our study include the robustness of the analysis of more than 1000 individuals with MM. The data come from the validated and externally monitored registry. The one problem that remains is the significance of uIFE in FLC-only myeloma. There is one report by Dejoie et al showing the importance of serum FLC rather than 24 hour urine FLC measurements in the assessment of response in FLC-only MM.[6] The prospective study for evaluation of the significance of uIFE in light chain MM and its significance in CR should be conducted. From the presented data, it could be concluded that prognosis of patients with uIFE not available is similar with those patients who are uIFE negative. There is also a highly significant difference between the VGPR group and CR and uCR group suggesting that patients with uIFE not available should not be marked as VGPR since their prognosis is nearing the CR group. Only very few patients have negative sIFE and positive uIFE and their time-to-events intervals are also similar to CR and uCR patients. Therefore, we suggest the patients with IIMM who lack uIFE results and otherwise fulfill CR criteria should not be marked as having VGPR.

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CONFLICT OF INTEREST

Authors declare no conflict of interest related to this work.

AUTHORS CONTRIBUTIONS

JR and TJ have designed the study and wrote the article. LP, IS, JM, TP, AJ, PP, LB, MS, FS, PH, VM, AH, MS, MW, PM PK, JU, and RH reviewed and approved the manuscript.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.