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Evaluation of Minimal Residual Disease using Next Generation Flow Cytometry in patients with AL amyloidosis

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INTRODUCTION

- Complete eradication of the plasma cell clone is of paramount importance in the treatment of patients with AL Amyloidosis but only a minority of patients will achieve deep hematologic responses.
- Undetectable detect minimal residual disease (MRD) may be associated with even better outcomes

AIM

- We aimed to to evaluate MRD in patients with newly diagnosed AL amyloidosis using sensitive next generation flow cytometry (NGF)

METHOD

- We used sensitive next generation flow cytometry (NGF) to detect MRD with a sensitivity of 2-3x10^{-6}.
- MRD was assessed in BM samples according to the Euroflow guidelines, using two independent 8-color panels, both containing CD19-PC7, CD27-BV510, CD38-FITC, CD45-PerCPCy5.5, CD56-PE, CD138-BV421, and additionally CD117-APC and CD81-APCC750 only in the surface tube or Cylgκ-APC and Cylgλ-APCC750 only in the intracytoplasmic tube.
- A median number of 5 million events (range 3.9x10^{6}-6.1x10^{6}) were acquired for each tube in a BD FACSCantoll cytometer and data analysis was conducted with Infinicyt software, that allowed merging of the two panels based on the 6 backbone markers, offering a median sensitivity level of 2.3x10^{-6} (range 2x10^{-6}-3.1x10^{-6}).

RESULTS

Baseline clinical characteristics of the cohort

	All patients n=126	MRDneg (n=46)	MRDpos (n=80)
Age (median, years)	63 (42-84)	62 (44-84)	64 (42-84)
Male/female (%)	52% / 48%	52% / 43%	51% / 49%
FLC type κ/ λ	16% / 83%	11% / 89%	20% / 80%
Cardiac involvement	95 (75%)	32 (70%)	63 (78%)
Renal involvement	85 (67%)	32 (70%)	53 (66%)
Liver involvement	26 (21%)	8 (17%)	18 (22%)
Mayo stage 1/2/3A/3B	19%/45%/24%/12%	17%/39%/26%/17%	19%/48%/23%/10%
NTproBNP (median, pg/ml)	2471 (20.9-44916)	2545 (20.9-44916)	2431 (65.3-29567)
eGFR (MDRD) (median, ml/min/1.73m^2)	80 (8.8-199)	78 (8.8-153)	82 (8.8-199)
24hUrine protein	3367 (0-40000)	4370 (0-26224)	2824 (36-40000)
Renal stage 1/2/3	22%/64%/14%	15%/73%/12%	25%/60%/15%
BMPC	15 (0-90%)	11 (0-90)	15 (0-70)
t(11;14)	45 (48%)	15 (40.5%)	30 (53%)
dFLC at baseline (median, mg/L)	163 (0.6-7228)	183 (1.7-2645)	160 (0.6-7228)
dFLC at MRD assessment (median, mg/L)	4.15 (0.45-46)	5.4 (0.5-22.8)	3.87 (0.45-46)
dFLC<10 at MRD	88 (70%)	32 (70%)	56 (70%)
iFLC <20 at MRD	80 (64%)	31 (67%)	49 (61%)
Treatment			
Bortezomib-based	66%	61%	69%
Dara-VCD	28%	30%	27%
Dara-mono	5%	9%	2%
Alkylator	1%		2%

MRD detection in patients with AL amyloidosis after primary therapy

- A total of 126 patients were assessed from May 2016 to December 2023
- MRD assessment was performed, at least 6 months after treatment initiation, in patients who achieved hematologic VGPR or better, confirmed in two successive assessments.
- In 46 patients (37%) MRD was undetectable (MRDneg) and in 80 (63%) was detectable (MRDpos)
- Median time from treatment initiation to MRD testing was 9.1 months (3.22-69.6 months).
- Baseline characteristics (table) did not differ between MRDneg and MRDpos patients
- No baseline factors were identified that could predict MRD negativity.
- There was no significant association between MRD status and the presence of t(11;14) (p=0.254)

MRD and hematologic responses:

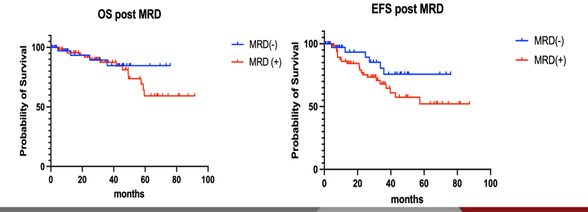
- More patients in the MRDneg group had CR (77% vs 49% of MRDpos, p=0.003).
- Nine patients, classified as hemVGPR were MRDneg (due to positive or absent immunofixation data).
- There was no association between MRD status and dFLC<10 mg/L or iFLC<20 mg/L at best response
- dFLC was <10 mg/L in 70% of patients who were MRDneg vs 68% of patients who were MRDpos, (p=0.826) and iFLC was <20 mg/L in 75% of who were MRDneg vs 60% of patients who were MRDpos (p=0.108).

MRD and organ responses:

- Organ responses were comparable among the two groups (p>0.05), observed in 66% of patients.
- Cardiac response rate (at latest time point available for assessment) was 63.3% among those who were MRDneg and 63.5% among MRDpos patients (p=0.99).
- The cardiac response rates at 3 months were 43.3% vs 39.3% , at 6 months 61.5% v 52.6% and at 12 months 57.9% vs 76.2%.
- Renal response rate was 60% among MRDneg vs 47.2% among MRDpos patients (p=0.26).
- The renal response rates at 3 months were 34.5% vs 36.4% , at 6 months were 50% v 45.1% and at 12 months 39.1% vs 43.2%.
- As expected organ responses required more than one year to occur in a significant proportion of patients

Outcomes post-MRD assessment:

- Median follow-up after MRD was 30.9 months (0.3-91.6 months)
- 19 patients started subsequent treatment [n=2(5%) among those MRDneg vs n=17(23%) among those MRDpos, p=0.015].
- Median time to subsequent treatment after MRD positivity assessment was 22.3 months (6.83-42.81).
- Overall, 18 patients have died, 4 among MRDneg and 14 among MRDpos patients.
- 2-year Event free survival (EFS) defined as hemProgression, second line initiation or death, was 93% vs 76% for MRDneg vs MRDpos patients (p=0.09).
- The difference was more pronounced among patients who were in hemVGPR (100% vs 76%).
- There was however no statistically significant OS difference (median OS not reached, p>0.05).



CONCLUSIONS

- Our data support once again the feasibility and clinical applicability of assessment of MRD using NGF in patients with AL amyloidosis.
- MRD assessment should be performed in all patients who have achieved hemVGPR or better; as a small proportion of them will be MRDneg due to the limitations of immunofixation.
- Organ responses are comparable among all patients in CR whether MRD neg or pos.
- Achieving MRD-negativity has implications with regards to long-term outcomes, such as hematologic relapse, need for subsequent therapy and survival.

CONFLICTS OF INTERESTS

No relevant conflicts of interests to disclose.

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