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ORIGINAL ARTICLE

Azacitidine-lenalidomide (ViLen) combination yields a high response rate in higher risk myelodysplastic syndromes (MDS)—ViLen-01 protocol

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Abstract Azacitidine treatment is effective in higher risk MDS (HR-MDS), with less than 50 % response, lasting 2 years. Aza and lenalidomide (Len) have a potential synergistic effect. ViLen-01 phase IIa trial includes 6-month induction (Aza 75 mg/m^2/day, days 1–5, Len 10 mg/day, days 6–21, every 28 days), 6-month consolidation (Aza 75 mg/m^2/day, days 1–5, every 28 days), and 12-month maintenance (Len 10 mg/day, days 1–21, every 28 days). Response was evaluated according to IWG criteria. Totally, 25 patients enrolled, with an average of 76.3 years old (60–87), and 88 % with major comorbidities. Thirteen patients completed induction, 7 proceeded for consolidation, and 2 for maintenance. The overall response rate (ORR) was 72 % (18/25), with 6 (24 %) for CR, 3 (12 %) for marrow CR, and 9 (36 %) for hematologic improvement (HI). The 7 non-responding patients were on the study 3 days to 4.1 months. At 6 months, 4 of 6 evaluable patients achieved complete cytogenetic response and 2 with del (5q) at diagnosis. Adverse events (AEs) were as expected in these patients: grades III–IV, mainly hematologic—thrombocytopenia (20 patients) and neutropenia (13 patients). The common non-hematologic AEs were infections (14 patients), nausea (7), vomiting (7), diarrhea (7), and skin reactions (5). The median progression-free survival (PFS) was 12 ± 1.36 months, with median overall survival (OS) of 12 ± 1.7 months. Quality of life (FACT questionnaire) data were available for 12 patients with a tendency towards improved QoL. This trial with elderly HR-MDS patients with an expected poor prognosis demonstrates a high (72 %) response rate and a reasonable expected safety profile but a relatively short PFS and OS.

Keywords Myelodysplastic syndromes · Azacitidine-lenalidomide · High-risk MDS

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Introduction

Hypomethylating agents (HMA), especially azacitidine (Aza, Vidaza^R), are the first-line treatment in higher risk (HR) MDS with a survival advantage [1, 2]. However, the overall response rate (ORR) is only 44 %, with a complete response of 14 % [3, 4] and a response duration of approximately 2 years (1–3). Once the patient fails on HMA, the prognosis is dismal with a median survival less than 6 months (3).

For patients who are refractory to or have relapsed after HMA therapy, there are few therapeutic options (3). The purine nucleoside clofarabine produced responses in approximately 30 % of such patients. Other possibilities include low-dose cytarabine or AML-type induction therapy, with expected response of about 50 % of those seen in similarly aged de novo AML cohorts. Among the tested investigational agents are rigosertib, a Ras mimetic agent that inhibits the PI3 kinase and PLK cellular signaling pathways, and sapacitabine, a purine analog. No second-line therapy has demonstrated a survival advantage over any other therapy or compared with supportive care.

Since Aza has been accepted as the standard first-line agent, several Aza-based combinations have been tested. Histone deacetylase inhibitors (HDACi) such as vorinostat and entinostat, combined with Aza, showed initial encouraging responses but later on, it became clear that they provided no advantage over Aza monotherapy (3). Navada et al. [5] have recently reported a marrow response rate of 65 % in patients who had failed on HMA, in a phase II trial, combining Aza with oral rigosertib.

Lenalidomide (Len, Revlimid^{R}) is effective in lower risk (LR) MDS, with [6–9] and without del (5q) [10, 11]. Len also has activity in HR-MDS and AML [12–14].

Aza-Len combination is an attempt to capitalize on the possible in vivo synergism that could be achieved by targeting both the bone marrow microenvironment and cell regulatory mechanisms that likely play a role in disease evolution [3, 15]. This was the rationale for several similar clinical trials [15–18], including ours. This combination was evaluated more than other Aza-based combinations and compared to Aza monotherapy. Several clinical trials have tested the safety, toxicity, and efficacy of the combination Aza-Len in this elderly high-risk patient population. Unfortunately, the small number of patients and the various study designs does not allow drawing definitive conclusions.

Sekeres et al. [15] treated 36 MDS patients with Aza-Len and achieved 72 % ORR, with 44 % CR. Finelli et al. [19], in a phase II trial, treated 19 patients with concomitant Aza-Len combination and 21 with sequential Aza-Len, with only 59 % ORR. The Australian team treated 160 patients with Aza-Len with ORR of 69 %, compared with 56 % with Aza monotherapy [20]. However, patients on Aza-Len had an inferior OS at 12 months, probably due to toxicity. A similar phase I/II sequential therapeutic regimen in MD Anderson Cancer Center with 88 HR-MDS and AML patients yielded only 35 % ORR and median OS of 75 weeks and significant toxicity, mainly myelosuppression [21]. The GFM conducted a phase I/II trial in 35 patients, with sequential Aza-Len combination and escalating doses of Len [22]. The median number of cycles received was only 2 and ORR was 20 %. Similarly, Narayan et al. [23] administered sequential Aza-Len to 32 previously treated MDS/AML patients. The median number of given cycles was 2, the ORR was only 25 %, and OS of responders was 9.8 months. Sekeres et al. have recently updated the results of The North American Intergroup Study SWOG S1117 [24]. In this phase II trial, 277 patients were randomized to receive Aza monotherapy vs Aza-Len concomitant combination vs Aza-vorinostat. The median duration of treatment was 22 weeks, and ORR was similar in all 3 arms; although there was a tendency towards a longer response with the combination treatment. Aza-Len combination yielded a higher rate of HI than Aza alone (16 vs 5 %). Aza-Len combination was also found to be superior in CMML patients: 63 % ORR compared with only 29 % with Aza monotherapy. The OS was similar: 17 months for Aza-Len compared with 15 months in Aza-treated patients. Again, combination treatment required more dose modifications.

The Israel MDS Working Group (MDS-WG) updates here the outcome of a phase IIa clinical trial, testing the efficacy and safety of Vidaza and Len, the ViLen combination, in these patients [25].

Methods

The ViLen-01 (Vidaza-lenalidomide) is an investigator-initiated multicenter phase IIa prospective single-arm open-label protocol of 3 stages. Inclusion criteria were intermediate (Int)-2 or high-risk MDS, according to the International Prognostic Scoring system (IPSS), termed higher risk (HR) MDS [26]. In addition, patients with Int-1 IPSS were included if they fulfilled one of the following poor prognostic criteria: RBC transfusion dependence, erythroid stimulating agent (ESA) resistance, or adverse cytogenetics. Patients who had previously been on Aza were allowed to join the protocol, assuming that the combination might be beneficial. The protocol was approved by local and national ethics committees, and patients provided signed informed consent. The protocol was listed as NIH trial TASMC-10-MM-0437-09-CTIL.

The 6-month induction phase consisted of 6 cycles of sc Aza, 75 mg/m^2/day, days 1–5, oral Len, 10 mg/day, days 6–21, followed by a 7-day respite. Patients who completed induction proceeded to a 6-month consolidation—Aza, 75 mg/m^2, days 1–5. After consolidation, patients continued to 12-m maintenance—Len 10 mg/day, days 1–21. Given the expected toxicity of both agents, we preferred sequential rather than concomitant administration. Also, the toxicity concerns limited the administration of Aza to 12 months (cycles) only.

Dose reduction levels were defined and implemented for cytopenias. In the case of grade IV neutropenia or thrombocytopenia, the study drug was withheld until recovery to grade ≤III and dose level reduction of both drugs was recommended. Aza dose was reduced from 75 mg/m^2/day × 5 days (level 0) to 50 mg/m^2/day × 5 days (level 1), 25 mg/m^2/day × 5 days (level 2), and 25 mg/m^2/day × 3 days only (level 3). Len dose was

reduced from 10 (level 0) to 5 mg/day (level 1), 5 mg qod (level 2), and 5 mg biw (level 3). Neutropenia and/or thrombocytopenia grade IV at level 3 required permanent drug discontinuation.

Response was evaluated according to the International Working Group (IWG) criteria [27]. The primary endpoint was ORR, including complete response (CR), marrow response (mCR), partial response (PR), and hematologic improvement (HI). HI could be isolated erythroid (HI-E), neutrophil (HI-N), or platelet lineage (HI-P) or combined. Secondary endpoints were safety, complete cytogenetic response, progression-free survival (PFS), and overall survival (OS). If the patient was alive, no progression was known, or information was missing, the PFS/OS was censored at the date of study completion (March 2, 2015). PFS/OS statistical analysis was performed by the Kaplan-Meier model.

Quality of Life (QoL)

The FACT questionnaire [28] was selected as the most acceptable and recognized tool. The questionnaire relates to physical, social, emotional, and functional well-being and includes an anemia subscale. The total cumulative score per patient reflects his perception, i.e., a higher score indicates a better QoL. Patients were asked to fill the questionnaire at baseline and after 4, 6, 12, and 24 months and the data were compared and analyzed.

Results

Figure 1 shows the patient disposition, with 37 patients screened, of whom 28, from 7 hospitals, were enrolled. Two patients were found on day 1 to be ineligible, and another preferred stem cell transplant (SCT). Thus, 25 patients comprise the study population. Adverse event (AE) and QoL were analyzed for all 28 patients.

The patient characteristics are presented in Table 1. The mean age was 76.3±7.4 years (60–87), with 17 (68 %) men and 8 (32 %) women. Eight patients (32 %) were >80 years. Comorbidities (CM) were recognized in 24 patients (96 %), and 22 (88 %) had major CM, mainly cardiovascular diseases. More specifically, patients suffered from diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, atrial fibrillation, recurrent strokes, and chronic lung disease. Four patients had 3 major CM, 4 others had 2 major CM, and a single patient had 4 major CM.

Two patients had no mitosis in their marrow samples. Fourteen patients (52 %) had favorable IPSS cytogenetics, including normal karyotype (9 patients) and del (5q) only (3). One patient had intermediate risk, and 8 had poor karyotypes.

Sixteen patients (64 %) were classified as Int-2 IPSS, 6 (24 %) had high-risk MDS, and 3 (12 %) had Int-1 MDS with poor prognostic feature(s). The common prior treatments were ESA (8 patients), thalidomide (2), and Aza (2 patients). Nineteen patients (76 %) were RBC transfusion dependent and 9 had received RBC only. Five patients (20 %) were treatment naïve.

Thirteen patients (52 %) completed induction (Fig. 1). The reasons for withdrawal were death due to unrelated CM (3 patients), drug toxicity (cytopenias in 3 patients: patient 19 neutropenia, patients 7 and 23 both neutropenia and thrombocytopenia), general deterioration (2), AML transformation (2), progressive disease (PD, 1), and investigator decision (patient 12 with CMML was given hydrea, a protocol violation and withdrew). Of the 13 patients who went on to consolidation, 8 (32 %) completed that phase and proceeded to maintenance. The reasons for consolidation discontinuation were AML transformation (2), death due to unrelated CM (2), and investigator decision after obtaining response (patient 10 achieved HI and was offered SCT). Only 2 patients completed the 2-year full protocol, with 6-month follow-up. Six patients did not complete maintenance, due to PD (3), patient decision (2, patients 1 and 18 both were requested to lower doses and believed that the low dose would not be effective), and general deterioration (1).

The study duration for the entire group was 3 days to 29.4 months (3–911 days), with a median of 6.3 months (191 days). Seven patients did not complete 4 cycles.

AEs were as expected in these patients. As a part of MDS, grade I–II cytopenia was not recorded. Anemia was recorded only if required RBC transfusions and/or hospitalizations. Grade III–IV AEs were mainly hematologic and as expected: thrombocytopenia (20 patients) and neutropenia (13). Non-hematological AEs included infections (14 patients, including pneumonia—4 and septicemia—4), nausea (7), vomiting (7), diarrhea (7), and skin eruption or pruritus (5). Other AEs were rare and unrelated to the disease or treatment. Dose reduction per protocol was applied in 20 patients (data not shown). Two patients were on protocol for less than a month and did not reach the second therapeutic cycle, in which the dose could be reduced. Thus, only 3 patients were treated for 191, 242, and 519 days without requiring a dose reduction.

Overall response rate (ORR) was 72 %—18 of 25 patients (Table 2). Six patients (24 %) achieved CR and 3 (12 %) marrow CR (mCR), totalling 9 patients (36 %) with CR/mCR. Nine patients demonstrated hematologic improvement (HI): 3 with uni-lineage HI (HI-E −1 patient, HI-N-1, HI-P-1). The other 6 HI were bi-lineage: HI-E + HI-N (3), HI-E + HI-P (2), HI-N+ HI-P (1). The 7 non-responding patients were on the protocol from 3 days to 4.1 months (median 3 months). Of note, of the two patients who had received Aza monotherapy prior to enrollment, patient 3 stayed on protocol 3 days only and patient 21 achieved hematological improvement (HI).

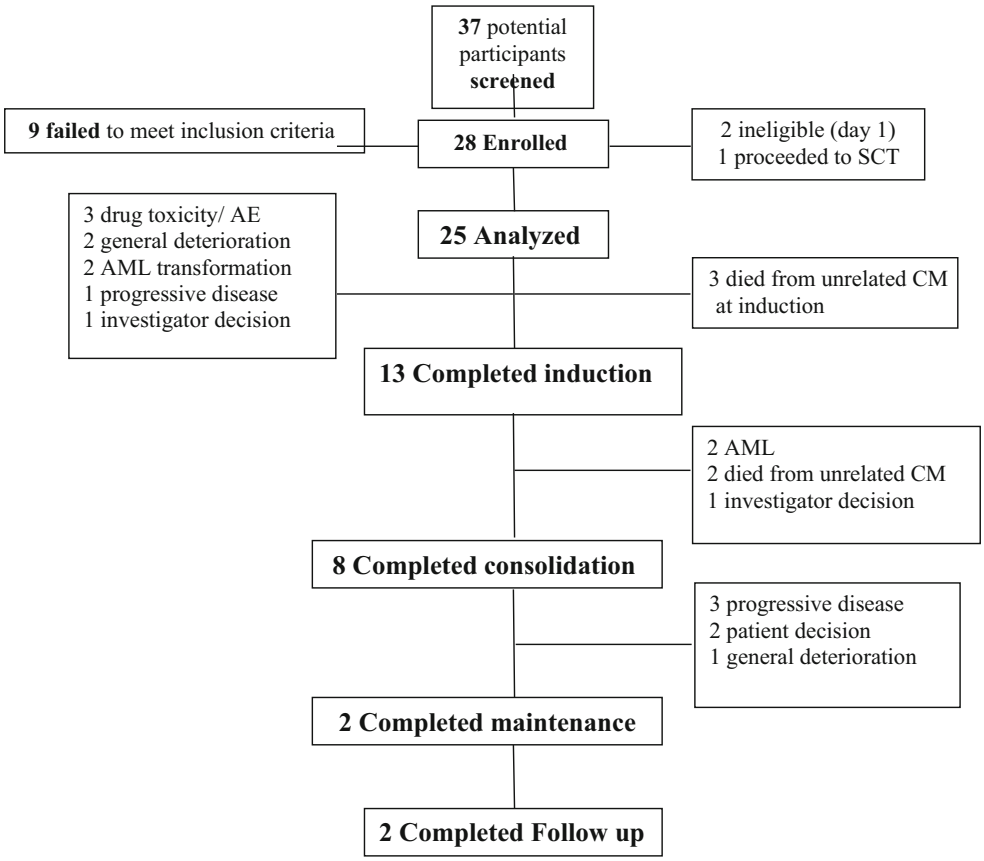

Fig. 1 Patient disposition

Cytogenetics could be analyzed in only 6 patients. This made it difficult to draw conclusions. However, of note, 4 of the 6 evaluable patients at 6 months achieved a complete cytogenetic response (Table 3). All 4 responders also demonstrated a clinical response. The reasons for no 6-month cytogenetics in 19 patients were (Tables 1, 2, and 3): Six patients did not reach the 6-month point of repeat cytogenetics; 4 had a normal karyotype at presentation; 6 patients with normal karyotype at presentation did not complete induction; 2 patients had no mitosis at presentation. A single patient with a complex karyotype at presentation achieved HI and was eligible for repeat 6-month cytogenetics but unfortunately did not undergo the test. One of the 2 patients with del (5q) only obtained cytogenetic response. Patient 4, with del (5q) and trisomy (+8), also achieved a cytogenetic response. Of note, 9/14 patients with favorable cytogenetics showed a clinical response, including 5 CR/mCR (Tables 2 and 3).

The median PFS was 12 ± 1.36 months. The probability of being progression free at 6 months was 0.79 (95 % CI [0.57–0.91]), at 12 months was 0.44 (95 % CI [0.22–0.63]), at 24 months was 0.20 (95 % CI [0.06–0.41]), and at 36 months was 0.10 (95 % CI [0.01–0.33]). The median OS was 12 ± 1.7 months. The probability of being alive at 6 months was 0.72 (0.5 % CI) [0.50–0.80], at 12 months was 0.48 (95 % CI [0.28–0.660]), at 24 months was 0.38 (95 % CI [0.18–0.57]) and at 36 months was 0.28 (95 % CI [0.10–0.51]).

Quality of life (Table 4)

Data from at least 2 time points were available for 12 patients. Others were not assessed because of treatment withdrawal or refusal. At 4 months, 6 patients demonstrated an increased score, totalling +212 points from baseline. Six other patients decreased their score totally by −93 points. Thus, the 4-month net change is an increase of +119 points or a mean of +9.9/patient. Additional time points could not be analyzed. When we compared the last score for each patient with baseline, we found that 7 patients increased their score, totally by +232, 4 patients had lower score, totally by −171, and a single patient had no change. Thus, for these 12 analyzed patients, there was a cumulative increase of +61 points, a mean of +5.1/patient, suggesting a mild QoL improvement. Correlating QoL with clinical outcome was difficult. However, 6/7 patients with improved QoL also demonstrated a clinical response.

Table 1 Patient characteristics

Patient number	Medical center	Age	Gender	Cytogenetics	IPSS/WHO	Prior Rx	RBC dependence
1	Rabin	63	F	del (5q)	LR/RCMD	Epo,	+
2	WGH	79	F	Complex + 5q	Int-2/RCMD	Epo, Len	+
3	"	86	M	Normal	HR/RAEB2	Aza	+
4	Kaplan	86	F	del (5q) + (+8)	Int-2 /RAEB2	Epo	+
5	"	76	F	Normal	Int-2 /RAEB2	–	+
6	"	84	M	Normal	Int-2 /RAEB2	–	+
7	"	75	F	del (5q)	HR/RAEB2	–	+
8	Rambam	72	M	No mitosis	LR/CMML	–	+
9	"	77	F	del (5q)	LR/del (5q)	Epo, Thal, Len	+
10	"	60	F	Complex + 5q	HR/RAEB2	–	+
11	"	73	M	Normal	HR/RAEB2	None	–
12	"	70	M	Normal	Int-2/CMML	HU	–
13	TASMC	82	M	Normal	Int-2/RAEB2	Epo, Thal	+
14	"	87	M	Trisomy +8	Int-2/RAEB2	Epo	+
15	"	78	M	del (20q)	Int-2/RAEB2	Epo	+
16	"	84	M	Complex	Int-2/RCMD	–	+
17	"	82	M	Complex	Int-2/RAEB1	Epo	+
18	"	67	F	Normal	Int-2/RAEB2	None	–
19	"	79	M	Normal	Int-2/RAEB2	None	–
20	"	79	M	Trisomy + 21	HR/RAEB1	–	+
21	"	70	M	Normal	Int-2/RAEB2	Cy, SCT, Aza	+
22	"	82	M	-Y	Int-2/RAEB1	–	+
23	"	77	M	Complex + 5q	HR/RAEB2	None	–
24	"	63	M	No mitosis	Int-2/RAEB2	None	–
25	"	78	M	Complex	In2/RCMD-RS	–	+
Mean		*76.3*					
Range		60–87	*17M/8F*				

WGH Western Galilee Hospital, *TASMC* Tel Aviv Sourasky Medical Center, *IPSS* International prognostic scoring system, *WHO* the classification, *Rx* treatments, *Thal* thalidomide, *HU* hydroxy urea, *Cy* cyclosporine

Discussion

Hypomethylating agents (HMA) like Aza are the standard therapy for HR-MDS [1–4]. However, the response rate is less than 50 %, with a median OS of 2 years. Non-responders have dismal prognosis, with OS of a few months [3, 29, 30]. Thus, a more effective novel approach is required. Len is effective in LR-MDS [6–11], HR-MDS, and AML [12–14, 31, 32].

Several clinical trials, with relatively a small number of patients, tried to apply the possible synergistic effects of these two agents in an attempt to improve the clinical outcomes [15–18]. The Israel National ViLen protocol is such an attempt of Aza-Len combination in patients with HR-MDS.

Our results, 72 % ORR and 24 % CR, are in line with other reports of small phase I–II Aza-Len combination in HR-MDS. The combination is synergistic with a higher response than obtained with either drug alone. As mentioned, and given the limitations and the small number of patients, cytogenetic interpretation is difficult, but of note, 9/14 patients with baseline favorable cytogenetics demonstrated a clinical response. The cytogenetic response in 4/6 analyzable patients further supports the clinical-karyotype correlation. Two of 4 cytogenetical responders had del (5q), consistent with reports on response with Len [4–7]. Finally, despite the small patient number, improved QoL is suggested, possibly with a clinical correlation.

Despite the encouraging results, Aza-Len combination raises several questions that need to be addressed. Why, despite the high ORR, the response duration as well as the OS were so short? Toxicity in these fragile patients appears to be a reasonable explanation. Indeed, in previous Aza (and decitabine) studies, approximately 50 % of patients developed common toxicity criteria (CTC) grade III or IV cytopenia [1, 3, 33]. Thus, it is not surprising that in the presented trial, 20 patients (80 %) required dose reduction and 23/25 (92 %) did not complete the protocol.

Table 2 Patient response

		HI				CR/mCR		
Patient number	Duration (month)	E	N	P	HI-E/N/P	CR	mCR	ORR
1	15.2	+	+	−	HI	–	–	Yes
2	10.1	+	−	+	HI	–	–	Yes
3	0.1	−	−	−	–	–	–	–
4	7.9	+	−	−	IR	CR	–	Yes
5	29.4	+	−	+	IR	CR	–	Yes
6	14.6	+	−	+	IR	–	mCR	Yes
7	2.0	+	+	−	HI	–	–	Yes
8	30.3	+	−	−	IR	CR	–	Yes
9	14.6	+	−	−	HI	–	–	Yes
10	6.3	+	−	+	HI	–	–	Yes
11	1.2	−	−	−	–	–	–	–
12	0.4	−	−	−	–	–	–	
13	9.2	+	−	+	IR	CR	–	Yes
14	4.1	−	−	−	–	–	–	–
15	3.0	−	−	−	–	–	–	–
16	3.9	−	+	−	HI	–	–	Yes
17	5.4	+	+	−	HI	–	–	Yes
18	17.1	−	+	−	IR	–	mCR	Yes
19	3.8	−	−	−	–	–	–	–
20	1.9	−	−	+	HI	–	–	Yes
21	3.4	−	+	+	HI	–	–	Yes
22	11.8	−	+	+	IR	CR	–	Yes
23	3.9	−	−	−	–	–	–	–
24	7.2	−	+	+	IR	CR	–	Yes
25	9.5	−	−	−	IR	–	mCR	Yes

ORR = CR + mCR + HI. For patients achieving CR/mCR, HI was irrelevant (IR)

The median duration on study was 191 days. Seven patients did not complete 4 cycles, missing the opportunity to respond to Aza, which requires 4-month exposure [1, 3, 33]. It is conceivable that not only the nature of high-risk disease and the aggressive therapeutic approach but also factors such as older age and the fragility of this patient population with associated CM contributed to the short PFS and OS despite the high ORR. A better patient

Table 3 Cytogenetic response (at 6 months)

Patient number	Cytogenetics at time 0	Cytogenetic risk group[a]	Cytogenetic response at 6 months	Clinical/hematological response	
				CR/mCR	HI
1[b]	del (5q)	Good	No		HI
2	Complex + 5q-	Poor	No		HI
4	del (5q) + (+8)	Poor	Yes	CR	
9	del (5q)	Good	Yes		HI
22	-Y	Good	Yes	CR	
25	Complex	Poor	Yes	mCR	

[a] Cytogenetic risk group—according to IPSS

[b] Patient 1 presented with del (5q), achieved HI-E and HI-N, and lost the del (5q) clone but later gained a new del (7q) clone. Thus, she was defined as a cytogenetical non-responder

Table 4 QoL—FACT score

Patient number		FACT scores						QoL net change		Clinical
	Time 0	4 months			6 months	12 months	24 months	+	−	
		Score	+	−						
1	112	110		−2	159	168		+56		HI
2	119	140	+21					+21		HI
5	82	94	+12		94	97	94	+12		CR
6	139	132		−7	151			+12		mCR
7	51	154	+103					+103		HI
9	107	134	+27		113			+6		HI
14	143	100		−43	96				−47	–
20	136	119		−17	117				−19	HI
23	104	85		−19					−19	–
24	146	159	+13		60				−86	CR
25	142	137		−5	151	142		0	0	mCR
26*	75	111	+36		97			+22		IR
Total (sum)			+212	−93				+232	−171	

Time 0 indicates the FACT score at presentation. The other time points were 4, 6 (end of the induction), 12 (end of the consolidation), and 24 months (end of study)

At 4 months, 6 patients increased their score by a total of +212 points, while other 6 patients decreased their score by a total of −93 points. The net change at 4 months was +119 points or a mean of +9.9 points per patient

The QoL net change shows individual difference of the FACT score between the last score recorded and the score at time 0. Thus, 7 patients increased their score with a total cumulative score of +232 points, 4 patients demonstrated together a decrease of −171 points, and for a single patient the last score was the same as at time 0. Thus, the final net change was +61 points, a mean of +5.1 points/patient

*Patient 26 was recruited but did not participate in the study (Fig. 1). He was not analyzed for response (irrelevant, IR) but was analyzed for QoL

A positive correlation is suggested between a clinical response and QoL

selection, dose modification, shorter treatment duration, and possible personalized regimen tailoring might improve tolerability and prolong the response in future trials with this treatment combination.

In conclusion, Aza-Len combination in HR-MDS patients resulted in high (72 %) ORR, but a short response duration, with substantial toxicity. Future trials, based on better understanding of the biology, will hopefully lead to better patient outcome.

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Compliance with ethical standards

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