An objective assessment in newly diagnosed multiple myeloma to avoid treatment complications and strengthen therapy adherence

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Abstract

In heterogeneous multiple myeloma (MM) patients treatment decisions are challenging. The hypothesis was that adaptation of treatment intensity (dose reduction [DR] *vs*. none) according to an objective risk score (revised-myeloma comorbidity index [R-MCI]) rather than physician judgement alone may improve therapy efficacy and avoid toxicities.
We performed this study in 250 consecutive MM patients who underwent a prospective fitness assessment at our center, after having received induction protocols based on physicians' judgement. DR, serious adverse events (SAE), response, progression-free survival (PFS) and overall survival (OS) were compared in fitness (fit, intermediate-fit, frail), age (<60, ≥70 years [y]) and therapy intensity subgroups at baseline and follow-up. Fit and <60 y patients were mostly treated with full intensity, whereas frail and ≥70 y patients usually received DR. Hematological and non-hematological SAE were more frequently seen in frail *versus* ≥70 y patients. Dose adaptations were mainly necessary in frail patients. OS and PFS were similar in fit and intermediate-fit but significantly worse in frail patients (P=0.0245/P<0.0001), whereas in age-based subgroups, OS and PFS differences did not reach significance (P=0.1362/P=0.0569). Non-hematological SAE were another negative predictor for impaired OS and PFS (P=0.0054/P=0.0021). In the follow-up performed at a median of 11 months after the first fitness assessment, the R-MCI improved or remained stable in 90% *versus* deteriorated in only 10% of patients. In conclusion, separation by R-MCI/frailty-defined subgroups was superior to age-based subgroups and can be used to improve tailored treatment. Fitter patients benefit from intensive therapies, whereas frail patients bear a need for initial DR.

Introduction

Multiple myeloma (MM) is a hematological disease, which typically affects elderly patients.[1] In the past decade, treatment options have substantially evolved and with inclusion of proteasome inhibitors (PI), immunomodulatory drugs (IMiDs) and antibodies (Ab)/immunotherapies into induction and relapse protocols, response rates, progression-free survival (PFS) and overall survival (OS) have improved impressively.[2] Standard treatment in newly diagnosed MM (NDMM) includes triplets or quadruplets, plus - if patients are deemed fit enough - autologous stem cell transplantation (ASCT), followed by maintenance therapy.[3,4] Even though patient assessment, via age, Karnofsky Performance Status (KPS), comorbidities, patient history and examination, is performed, MM patients' actual constitution and fitness can be over- or underestimated.[5-8] Additionally, inclusion in clinical trials is especially rare in elderly patients over the age of 70 years.[5,6] This suggests that more objective tools may assist physicians to find most suitable treatment regimens and to adapt dose intensity for elderly and/or MM-stricken patients.
In line, the long continuing COVID-19 pandemic imposes the need to prevent any unnecessary serious adverse events (SAE), hospitalization, time-consuming dose adjustments and therapy cessations.[9-13] However, therapy decisions are often made without an objective fitness as-

sessment.[7,14,15] In recent years, MM-specific risk scores (e.g., International Myeloma Working Group (IMWG)-frailty score, revised-myeloma comorbidity index (R-MCI), Mayo-risk score, UK Myeloma Research Alliance Risk Profile) were developed to assist in this unsolved matter.[16-19]

The hypothesis of this study was that adaptation of therapy intensity according to an objective risk score (via R-MCI; *Online Supplementary Figure S1*), rather than via physician judgement alone, may improve therapy efficacy and avoid therapy toxicities and discontinuation. More studies are now testing the feasibility of MM-specific risk-scores for treatment assistance in MM patients, albeit additional studies should further be performed.[14,20-22] We used the R-MCI, because this constitutes a repeatedly validated MM-specific risk tool, used routinely for MM patients at our institution, that has been integrated into our electronic tumor board (TB) online system.[17,23] The R-MCI contains of five weighted risk factors, namely renal and lung function, KPS, frailty and age, plus allows to include cytogenetics.[17,23] The R-MCI web tool allows the immediate calculation of the weighted R-MCI, which can be likewise performed by physicians or research assistants (www.myelomacomorbidityindex.org). We here investigated the applicability of the R-MCI for future therapy decision support by performing an analysis of patients receiving first-line treatment. Main aspects of this study were to track patients' induction treatment, comparing R-MCI- *versus* age subgroups in terms of therapy adaptations, SAE, response, OS and PFS.

Since patients' constitution and disease burden may change during treatment, we also re-evaluated constitution, fitness and R-MCI changes in a follow-up analysis (*Online Supplementary Figure S2*).

Methods

Data sources and study design

We performed this exploratory study in 250 consecutive MM patients, who received induction treatment ideally continuing until intolerance or progression at our Comprehensive Cancer Center Freiburg (CCCF) and catchment area of the Black Forest from 2000 to 2018. All patients were fully documented at our CCCF. The cohort with prospectively assessed R-MCI was pooled from two prior conducted analyses,[8,17] retrieving patient- and therapy-relevant data through our electronic documentation system 'Medoc'. Of the initial 359 patients, 109 had to be excluded either due to ongoing induction at the time of assessment (n=50) or incomplete data (n=59; *Online Supplementary Figure S2*). Patients' characteristics included the International Staging System (ISS), R-MCI and IMWG-frailty scores at baseline. Via R-MCI and IMWG-frailty scores, all patients were grouped as fit, intermediate-fit or frail (Table 1; *Online Supplementary Figure S1*). Decisions of induction regimen, treatment intensity and dose reductions (DR) were based on physicians' choice. Comparisons were performed for frailty- (R-MCI-fit, -intermediate-fit, *vs*. -frail), age- (<60, 60-69 *vs*. ≥70 years) and therapy-intensity (with *vs*. without initial DR) subgroups.

The study was performed according to the guidelines of the Declaration of Helsinki and Good Clinical Practice. All patients gave their written informed consent for institutionally initiated research studies and analyses of clinical outcome studies conforming to the institutional review board guidelines. The trial protocol was approved by the ethics committee of the University of Freiburg (EV 81/10).

Induction, dose reductions, serious adverse events, response and follow-up analysis

For each induction regimen, one lead agent was determined. Albeit any DR of any drug in combination first-line treatment could have been counted as a dose modification, this would not have allowed a less complex intensity calculation. Thus, any decrease in the lead agents' standard dose intensity or change from triplets to doublets was defined as DR. Lead agents were defined, with regard to the severity of adverse events (AE) in the following order of priority: alkylating agents, subsequently IMiDs and PI/Ab, last anthracyclines or glucocorticoids. The standard dose was consistent with NCCN/EMN-guidelines and CCCF-chemotherapy manual.[24]

We used the Common Terminology Criteria (CTC) for AE version 5.0 to assess grade 3-4 hematological SAE (anemia, leukocytopenia, thrombocytopenia) and non-hematological SAE grades 3-5 (infections, renal, pulmonary, cardiac impairment).

Quality of response was assessed via IMWG-remission criteria until the end of induction.[25,26]

Six to 24 months after the first fitness assessment, we analyzed, if changes in remission status and patients' constitution via a follow-up R-MCI analysis had occurred.

Statistical analysis

OS was defined as the time from start of induction to death from any cause and PFS as the time from start of induction to cancer recurrence or death from any cause. Data for patients alive at the time of the analysis were censored at the last follow-up. Probabilities of PFS and OS were estimated using Kaplan-Meier method and compared with log-rank tests. In order to avoid an immortal time bias, plots of OS and PFS of patients showing no or at least one SAE, included only those who survived at least 6 months after the start of induction treatment. Chi-square- and Mantel-Haenszel tests were utilized as appropriate in the comparisons of therapy protocols, DR, SAE, response rates in R-MCI and age groups. A *P* value of <0.05 was con-

sidered as statistically significant. Data were analyzed with SAS 9.2 (SAS Institute, Inc, Cary, North Carolina).

Results

Patient characteristics' and induction regimen

Among the 250 analyzed patients the median age at baseline was 62 years and 61% were males. For a cohort, where first-line treatment was mainly applied at a tertiary and referral center, patient characteristics were typical (Table 1), likewise myeloma subtypes, ISS, median bone marrow infiltration (45%) underlying AL-amyloidosis rate (6%), and cytogenetics. ISS stage 2 and 3 were most common with 66% (Table 1).

Median IMWG-frailty score and R-MCI were 1 and 4, respectively, in line with prior test and validation analyses.[15,17,23,27,28] Impaired constitution via KPS ≤70% was present in 42% and moderate or severe frailty was reported in 36%.[8,17,23] Renal impairment with eGFR <60 mL/min/1.73m^2 was present in 40% and moderate or severe lung dysfunction as defined via R-MCI website in 12%, in line with previous analyses.[8,17,23,29,30]

VCD, VRd/RAD or other induction (*Online Supplementary Figure S3*) was predominantly performed with VCD and whenever possible in German study group (DSMM)-protocols (DSMM XI, XII, XIV).[31,32] Induction was often initiated at the CCCF, but also at regional hospitals and private practices. Stem cell transplantation (SCT) was performed in 72% (Table 1).

Comparisons of patient- and therapy-relevant parameters in entire cohort, and in revised myeloma comorbidity index, age and dose intensity subgroups

Patient and therapy parameters are summarized in Table 2 in entire cohort and in fit *versus* frail, younger *versus* older and full-dosed (no DR) and dose-reduced (initial DR) subgroups. No initial DR *versus* DR were performed in 59% and 41%, respectively, reflecting the complexity to treat an even fairly young MM cohort, and that initial DR was frequently performed. The number of hematological and non-hematological SAE were frequent with 157 and 123,

Table 1. Baseline multiple myeloma patient characteristics (n=250).

	N (%)	Median (range)
Age, years		62 (27-92)
Sex, male/female	153/97 (61/39)	
Myeloma subtype IgG/IgA IgM Light chain only/biclonal/asecretory K/λ/biclonal/asecretory	 131/47/2 (52/19/1) 64/2/4 (25/1/2) 160/88/1/1 (64/35/0.5/0.5)	
International Staging System, I/II/III	84/71/95 (34/28/38)	
Bone marrow infiltration, cytology/histopathology (%)		35/45 (0-90/0-100)
AL-Amyloidosis, yes/no	16/234 (6/94)	
Cytogenetics, favorable/unfavorable[*1]/ missing	109/112/29 (43.6/44.8/11.6)	
Comorbidity indices IMWG-frailty score: fit/interm./frail R-MCI: fit/interm./frail	 75/86/89 (30/34/36) 73/145/32 (29/58/13)	 1 (0-4) 4 (0-9)
KPS, 100/80-90/≤70%	15/130/105 (6/52/42)	
Frailty,[*2] no/mild:moderate/severe	160:90 (64:36)	
Renal function, EGFR ≥90/89-60/<60 mL/min	50/101/99 (20/40/40)	
Lung dysfunction,[*3] no/mild:moderate/severe	221:29 (88:12)	
Therapy induction VCD/VRD/RAD/other[*4] Place of induction: CCCF/others[*5] Performed SCT/non-SCT	 176/35/39 (70/14/16) 198/52 (79/21) 179/71 (72/28)	

IMWG: International Myeloma Working Group; interm.: intermediate-fit; R-MCI: revised myeloma comorbidity score; KPS: Karnofsky performance status; eGFR: estimated glomerular filtration rate; VCD: bortezomib, cyclophosphamide, dexamethasone; VRd: bortezomib, lenalidomide, dexamethasone; RAD: lenalidomide, adriamycin, dexamethasone; CCCF: Comprehensive Cancer Center Freiburg; SCT: stem cell transplant. [*1]Unfavorable: del17p13, t(4;14), t(14;16), t(14;20), chromosome 1 abnormalities, c-myc, del(13q14), hypodiploidy. [*2]Frailty[8,17,23]: Karnofsky Index ≤70%; Time Up/Go >10 seconds; IADL ≤4 points; subjective fitness grade E or F. [*3]Lung dysfunction: mild: FEV1 <80%; moderate: FEV1 ≤60% or diffusion capacity ≤61%, severe: FEV1 <50%; mild: 0/1 parameter is correct; moderate: 2 parameters are correct; severe: >2 parameters are correct. [*4]Others: proteasome inhibitors, antibodies, anthracyclines, glucocorticoids. [*5]Others: regional hospitals/private practices.

which accounted for SAE per patient in 0.63 and 0.49, respectively. The median induction duration was 62 days. Best IMWG response (≥ partial response [PR]) after induction was observed in 75% in line with prior data (Table 2).[31] Results of R-MCI fit and younger (<60 years) patients were similar and merely differed in used protocols and SAE (Table 2). Intermediate-fit and frail patients (combined: 71%) showed increased median ages of 66 and 74 years, respectively. VRd/RAD first-line treatment in fit, intermediate-fit and frail patients were performed in 37%, 15% and 6%, thus decreased with frailty, whereas DR substantially increased (19%, 45% and 72%, respectively; Table 2). In line, SAE per patient increased from 0.23 in fit, to 0.72 in intermediate-fit and 1.1 in frail patients for hematological SAE, and 0.23, 0.48 and 1.13 for non-hematological SAE. Median induction duration in intermediate-fit patients was similar to fit patients, basically because SCT in intermediate-fit patients remained considerable with 72%. As expected, in frail patients longer induction (6-9 cycles plus maintenance) was performed and less SCT (Table 2). Divided into fit, intermediate-fit and frail patients, the response rates were 73%, 77% and 69%, respectively, thus higher in both former than latter subgroup (Table 2).

According to age subgroups, DR increased in <60, 60-69 and ≥70-year-old patients from 21% to 43% and 66%, respectively. SAE per patients increased less and seemed less predictable than in R-MCI subgroups (Table 2). Transplant-eligible patients aged 60-69 years did hardly show any differences in non-hematological SAE compared to patients ≥70 years (0.58/patient *vs*. 0.62/patient). SCT frequencies were typical in young in 93%, 81% in 60-69 and 32% in ≥70-year-old patients. Transplant-ineligible patients (≥70 years) were at treatment initiation in 29 of 73 (40%) >75 years old. Best responses (≥PR) in age cohorts ranged from 66-79% (Table 2).

In dose intensity subgroups, for patients without *versus* with DR, median age differences and R-MCI-differences were notable with 58 *versus* 69 years and 4 *versus* 5, respectively. This was in line with lesser performed SCT in the latter group (Table 2). Whereas hematological SAE/patient were similar in patients without *versus* with DR, these almost doubled for non-hematological SAE (0.36 versus 0.69/patient, respectively). Median induction duration was similar in both groups, while as expected, response rates (≥PR) were increased in patients without DR (Table 2).

Table 2. Patient and therapy parameters in entire cohort, in revised myeloma comorbidity score, age and dose intensity subgroups.

	Entire group	Fit	Intermediate	Frail	<60 years	60-69 years	≥70 years	No initial DR	Initial DR
Patients, N (%)	250 (100)	73 (29)	145 (58)	32 (13)	101 (40.4)	76 (30.4)	73 (29.2)	148 (59)	102 (41)
Median age, years (range)	62 (27-92)	55 (29-77)	66 (27-85)	74 (61-92)	53 (27-59)	65 (60-69)	75 (70-92)	58 (29-80)	69 (27-92)
Median R-MCI (range)	4 (0-9)	3 (0-3)	5 (4-6)	7 (7-9)	3 (0-6)	4 (2-8)	6 (2-9)	4 (0-9)	5 (2-9)
Lead agents,[*1] N (%) Alkylating agents IMiDs Others[*2]	 190 (76) 51 (20) 9 (4)	 42 (57.5) 27 (37) 4 (5.5)	 119 (82) 22 (15) 4 (3)	 29 (91) 2 (6) 1 (3)	 71 (70) 24 (24) 6 (6)	 56 (73.7) 18 (23.7) 2 (2.6)	 63 (86.3) 9 (12.3) 1 (1.4)	 109 (74) 37 (25) 2 (1)	 79 (77) 12 (12) 11 (11)
Initial DR, N (%) No Yes	 148 (59) 102 (41)	 59 (81) 14 (19)	 80 (55) 65 (45)	 9 (28) 23 (72)	 80 (79) 21 (21)	 43 (57) 33 (43)	 25 (34) 48 (66)	 148 (100) 0 (0)	 0 (0) 102 (100)
Hematological SAE, N (per patient)	157 (0.63)	17 (0.23)	105 (0.72)	35 (1.1)	54 (0.53)	44 (0.58)	59 (0.81)	92 (0.62)	65 (0.63)
Non-hematological SAE, N (per patient)	123 (0.49)	17 (0.23)	70 (0.48)	36 (1.13)	34 (0.34)	44 (0.58)	45 (0.62)	53 (0.36)	70 (0.69)
Median induction duration, days (range)	62 (2-365)	61 (14-365)	61 (2-299)	80 (5-271)	59 (10-217)	62 (2-365)	78 (5-299)	61 (5-299)	65 (2-365)
Performed SCT, N (%)	179 (72)	68 (93)	104 (72)	7 (22)	94 (93)	62 (81)	23 (32)	126 (85)	53 (52)
Obtained best response, N (%) CR/vgPR/PR SD/PD	 187 (75) 63 (25)	 53 (73) 20 (27)	 112 (77) 33 (23)	 22 (69) 10 (31)	 79 (78) 22 (22)	 50 (66) 26 (34)	 58 (79) 15 (21)	 118 (80) 30 (20)	 69 (68) 33 (32)

DR: dose reduction; R-MCI: revised-myeloma comorbidity index; VCD: bortezomib, cyclophosphamide, dexamethasone; IMiDs: immunomodulatory drug; RAD: lenalidomide, adriamycin, dexamethasone; VRd: bortezomib, lenalidomide, dexamethasone; SAE: serious adverse event; SCT: stem cell transplant; CR: complete remission; vgPR: very good partial remission; PR: partial remission; SD: stable disease; PD: progressive disease. [*1]Lead agent prioritization was based on expected severity of adverse events; lead agents were rated: alkylating agents (mainly VCD) first, subsequently IMiDs (mainly RAD/VRd) and PI/Ab, and last anthracyclines or glucocorticoids; i.e., in VCD: cyclophosphamide was the lead agent. [*2]Others: proteasome inhibitors, antibodies, anthracyclines, glucocorticoids.

Serious adverse events: subgroup distribution for hematological and non-hematological serious adverse events

Distinct differences in types of hematological and non-hematological SAE are shown in Figure 1A and B, being more prevalent in frail than intermediate-fit or fit patients.

Anemia, leukocytopenia and thrombocytopenia SAE (CTC grade 3-4) occurred in 76, 56 and 25 patients, respectively. Leukocytopenia was equally prevalent in frail and intermediate-fit patients (44% and 45%, respectively), while anemia and thrombocytopenia were predominantly observed in frail patients (59% and 68%, respectively; Figure 1A). Hematological SAE appeared in patients

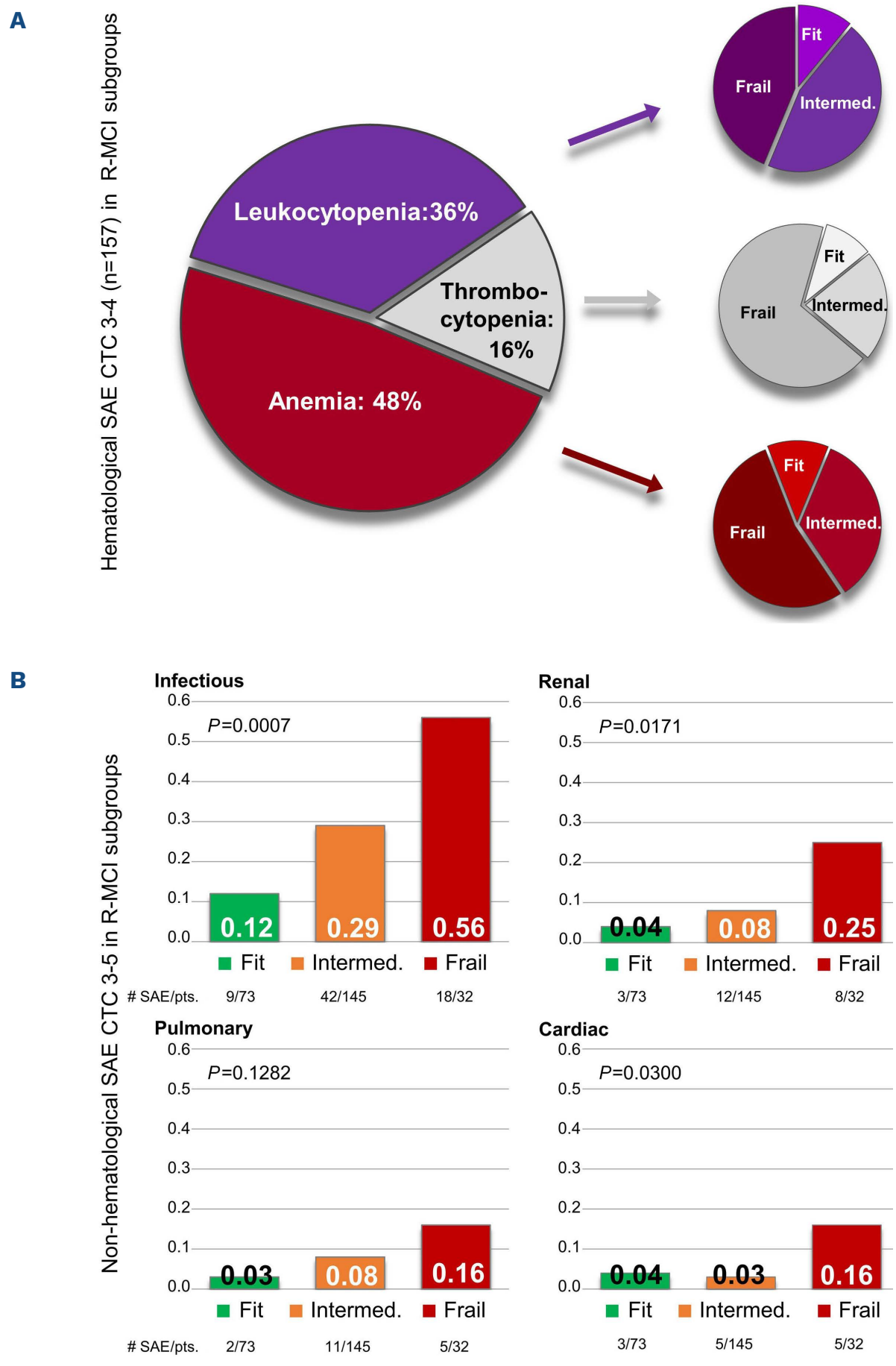

Figure 1. Serious adverse events in revised-myeloma comorbidity index subgroups. (A) Hematological serious adverse events (SAE) common toxicity criteria (CTC) 3-4: distribution in entire cohort and revised-myeloma comorbidity index (R-MCI) subgroups in percentage. Leukocytopenia: *P*=0.0008; thrombocytopenia: *P*=0.0007; anemia: *P*<0.0001. (B) Non-hematological SAE CTC grades 3-5 in R-MCI subgroups per patient. pt.: patient. Intermed: intermediate.

treated with alkylating agents (VCD) in 47% and with IMiD-based protocols (VRd/RAD) in 20% ('others' were too few for meaningful conclusions).
Of 123 registered non-hematological SAE, 69 were attributed to infectious, 23 to renal, 18 to pulmonary and 13 to cardiac causes (Figure 1B). Comparison of different R-MCI subgroups with infectious, renal, pulmonary and cardiac SAE showed significant increases in frail as compared to fit or intermediate-fit patients, reaching significance in all except pulmonary SAE (Figure 1B).

Therapy adaptations in frailty and age subgroups

Our assessment of SAE in patients without or with initial DR is depicted in the *Online Supplementary Table S1A and B*. The occurrence of hematological SAE without or with DR did not show distinct differences in frailty subgroups. Therapy adaptations (DR, therapy pauses or discontinuation) after hematological SAE occurred in intermediate-fit or frail patients only, both without and with performed initial DR (*Online Supplementary Table S1A*).
Non-hematological SAE occurred in R-MCI subgroups likewise more often in patients without DR than if performed, whereas this was less strikingly found for age subgroups (*Online Supplementary Table S1B*). Therapy adjustments or therapy discontinuations after non-hematological SAE increased both with frailty and age, and were more prevalent with full doses than if DR had been performed (*Online Supplementary Table S1B*).
Therapy discontinuation occurred in only eight of 250 (3%) patients (*Online Supplementary Table S2*), showing mostly advanced age and impaired R-MCI scores. Initial dose reductions had been performed in seven of eight patients. Patient constitution complications, myeloma- and/or therapy-induced complications occurred in already the 1st (n=3) to 4th (n=3) induction cycle (range, 1-4). Retrospectively assessed therapy intensity by us (MH, ME) suggested in seven of eight patients, that these were overdosed. Thus, if on top of clinical judgement, R-MCI-tailored therapy had been performed - SAE and therapy cessation might have been avoided in seven of eight patients.

Serious adverse events leading to early death (<60 days after induction) or concomitant serious adverse events

SAE during induction which led to death were seen in three patients (3/250 i.e., in 1.2%). These showed cardiac complications, two of three associated with underlying AL-amyloidosis. Sixteen patients with concomitant AL-amyloidosis contributed to 28% of cardiac (n=13) and renal (n=23) SAE (CTC 3-5) of the entire cohort, thus showed a 5.6 higher risk for these complications. As expected, patients with CTC grade 3-4 leukocytopenia were more likely to acquire severe infections (*Online Supplementary Table S3*).

Overall survival and progression-free survival of entire cohort and in various subgroups

The median follow-up from start of induction was 65 months (range, 1-246). Detailed response in fit, intermediate-fit and frail patients are summarized in the *Online Supplementary Table S4*. The Kaplan-Meier curves for OS and PFS analyses are displayed in Figures 2 and 3. The estimated 3-year OS and PFS in the entire cohort were 85% (95% confidence interval [CI]: 79-89) and 53% (95% CI: 47-60), respectively (Figure 2A and B). The three R-MCI subgroups in Figure 2C and D showed similar results for both fit and intermediate-fit patients. The 3-year OS in R-MCI fit, intermediate-fit and frail was 89% (95% CI: 79-94), 85% (95% CI: 77-90) and 70% (95% CI: 47-85), respectively (P=0.0688; Figure 2C). The 3-year PFS was 60% (95% CI: 47-70), 55% (95% CI: 47-63) and 21% (95% CI: 6-41), respectively (P<0.0001; Figure 2D).
Since results of fit and intermediate-fit patients were comparable and very different to frail patients, these were combined as displayed in Figure 2E and F. Of note, 3-year OS and PFS in fit/intermediate *versus* frail patients showed highly significant differences of 86% (95% CI: 81-90) *versus* 70% (95% CI: 47-85) and 57% (95% CI: 50-63) *versus* 21% (95% CI: 6-41), respectively (P=0.0245/P<0.0001).
Age subgroups revealed differences with best OS/PFS for <60-year-old patients, whereas 60-69 and ≥70-year subgroups revealed similar Kaplan Meier curves. Notably, 3-year OS/PFS results via age displayed lesser and insignificant group distinctions (P=0.1362/P=0.0569; Figure 2G and H).

Serious adverse events and dose reduction impact on overall survival and progression-free survival

Any SAE led to impaired OS and PFS (Figure 3A and B), both for hematological (Figure 3C and D) and non-hematological SAE (Figure 3E and F), with more striking OS and PFS differences for the latter SAE. In line, DR *versus* no DR led to both OS and PFS differences in favor of patients with no DR, reflecting standard doses to be easier applied in fitter and younger patients and therefore accounting for these differences (Figure 3G and H).

Revised myeloma comorbidity index follow-up analysis

The follow-up analysis (T0 → T1) was possible in 180 patients (72%; Figure 4; *Online Supplementary Figure S2*). The median follow-up was 11 months (range, 6-24), in line with our previous study.[8] Median R-MCI scores at T0 and T1 were both 4, reflecting intermediate-fit patients. Assessing also mean T0 *versus* T1 differences, the R-MCI improved from 4.3 to 3.7, respectively and accounted for a mean improvement of 0.6 points over an 11 month period (P<0.0001). Among all follow-up patients, 77 (43%) achieved a better, 84 (47%) a stable and only 19 (10%) a worse R-MCI (Figure 4). Maximum R-MCI changes were

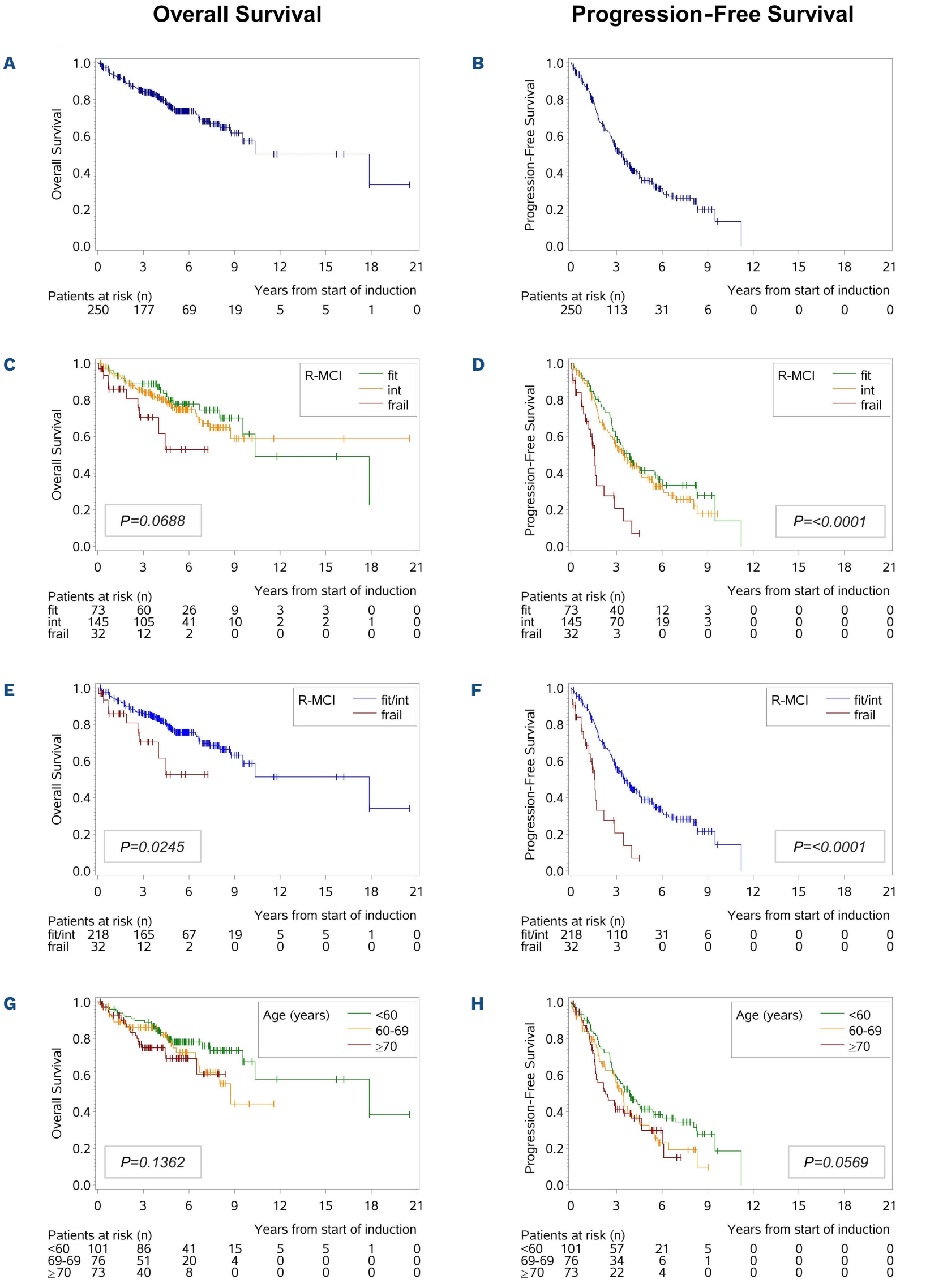

Figure 2. Kaplan-Meier plots for entire cohort and different risk group distributions. (A) Overall survival (OS) and (B) progression-free survival (PFS) in entire cohort. (C) OS and (D) PFS in revised-myeloma comorbidity index (R-MCI) subgroups. (E) OS and (F) PFS in R-MCI subgroups fit and intermediate-fit (Int) *vs*. frail. (G) OS and (H) PFS in age groups.

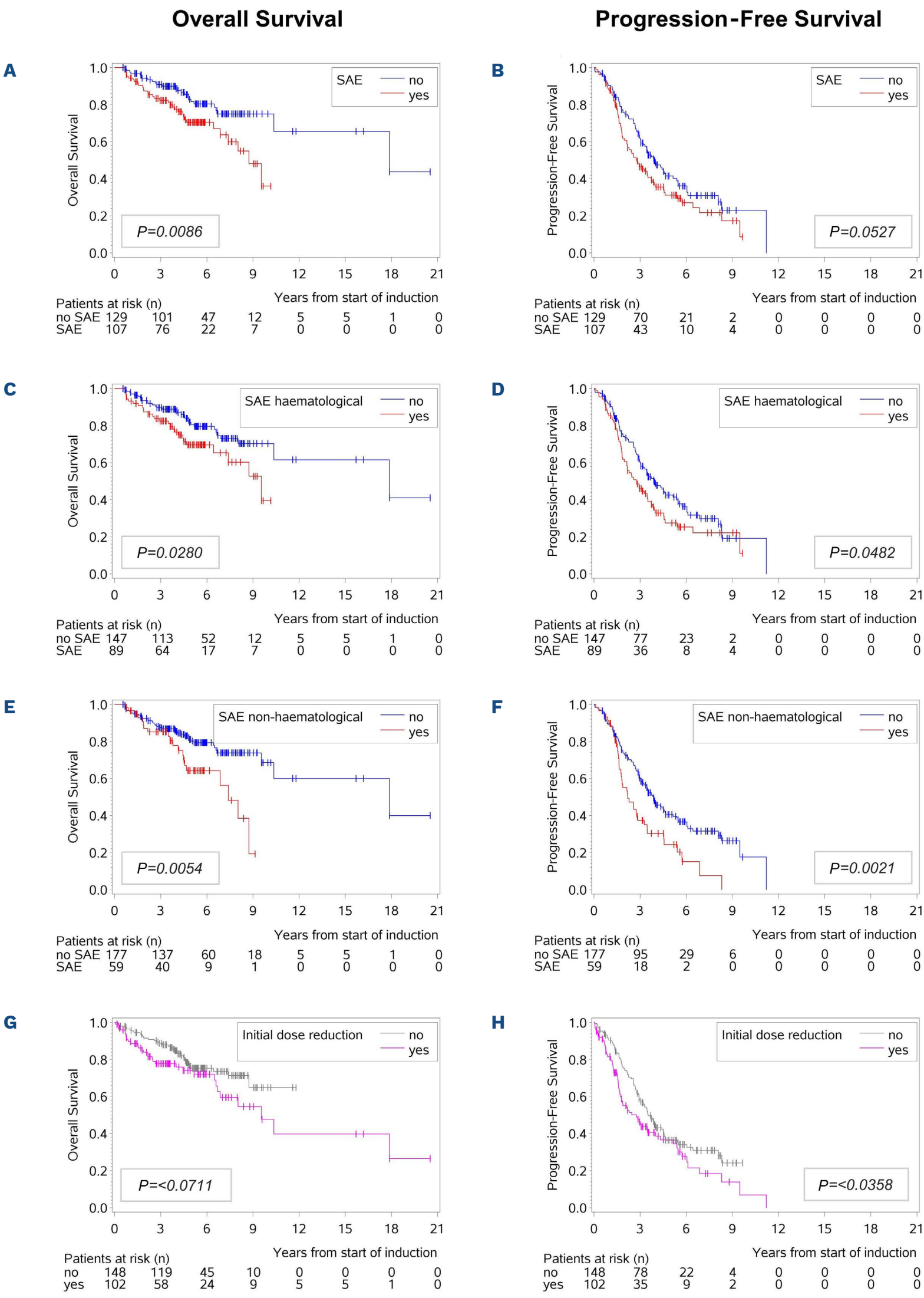

Figure 3. Kaplan-Meier plots for patients without or with serious adverse events and patients without or with initial dose reduction. (A) Overall survival (OS) and (B) progression-free survival (PFS) in patients without or with any serious adverse events (SAE). (C) OS and (D) PFS in patients without or with any hematological SAE. (E) OS and (F) PFS in patients with or without any non-hematological SAE. (G) OS and (H) PFS in patients with or without DR. R-MCI: revised-myeloma comorbidity index; SAE: serious adverse events dose reduction; DR: dose reduction.

improvements by four points (R-MCI 6 → 2) and deteriorations by three points (R-MCI 4 → 7), impressively illustrating that R-MCI changes within a ~1 year follow-up can be more drastic than age shifts within this period.

Discussion

One crucial aspect for MM patients and physicians is the individual selection of the initial (and subsequent) treatment and its intensity.[7,33] Our message is that we apply evidence generated from clinical trials that rarely include old or frail patients to treat such patients without knowledge of the need for modifications of the drugs used, the dosing or schedule. Although our study population received first-line MM treatment with dose modifications according to best clinical judgment and a prospective frailty assessment was performed, the frailty assessment was not used for decision making. Thus, clinicians were blinded to this information. This allowed to assign patients into those with *versus* without DR as compared to comorbidity and age subgroups (Table 2). Hence, we investigated physicians' therapy decisions in a NDMM population during induction by analyzing the course of therapy and patient outcome. Our data demonstrates that the use of the R-MCI can assist to anticipate the likelihood of SAE. Those predictions can subsequently be used to optimize induction dose intensity (Table 2; Figure 1A and B) and identify patients at risk of treatment discontinuation with the associated risk of a more unfavorable outcome (Figure 2 and 3). We found compelling differences between R-MCI subgroups regarding protocols and doses prescribed. Overall, alkylating agents were the most used leading agent, in line with VCD being a commonly applied DSMM/GMMG and EMN-study regimen.[31,34] With a median start of induction in 2016, most frail patients in our cohort were treated in compliance with guidelines for dose-adjusted VCD or Vd as first-line treatment.[34] The EHA-ESMO guideline from 2021 propagates nowadays to add a CD38-antibody (e.g., Dara-VMP, Dara-Rd) in NDMM patients ineligible for ASCT, reiterating that R-MCI- or other risk-tool-adapted triplets and quadruplets may profit from our approach described here to avoid SAE and therapy cessations.[33]

We were also able to show that patients at risk were mostly correctly identified and reasonable dose adaptations were made, but potential improvements remain. Moreover, we determined that fit patients had few initial DR (19%) and a low incidence of hematological or non-hematological SAE (both 0.14 per patient). In contrary, full-dosed frail patients (28%) were nine times more likely to suffer from hematological SAE and had a four times higher rate of non-hematological SAE (*Online Supplementary Table S1A and B*). The conjecture that some frail patients were possibly overtreated and dose-reduced fit patients undertreated is therefore plausible and has been described previously.[6,17,23,34] Besides, the 3-year OS was superior in frail patients with initial DR *versus* in frail patients without initial DR (73% *vs*. 63%). Although numbers of this subgroup comparison were limited, other studies confirm this observation.[11,22,35,36] Moreover, we observed that two of three events of death were associated with subclinically underlying AL-amyloidosis. These findings confirmed the need to critically evaluate induction protocols and proto-col doses to avoid therapy complications and to reliably detect AL-amyloidosis.[37,38] Indeed, the occurrence of any SAE was associated with a worse outcome (Figure 3A), validating prior studies.[11,36,37]

Since various treatment pathways continue to suggest age cut-offs (i.e., >60 or >70-years), we divided our cohort into patients aged <60, 60-69 and ≥70 years and compared them to R-MCI and therapy intensity (DR *vs*. no DR performed) subgroups (Table 2). In line with our and other

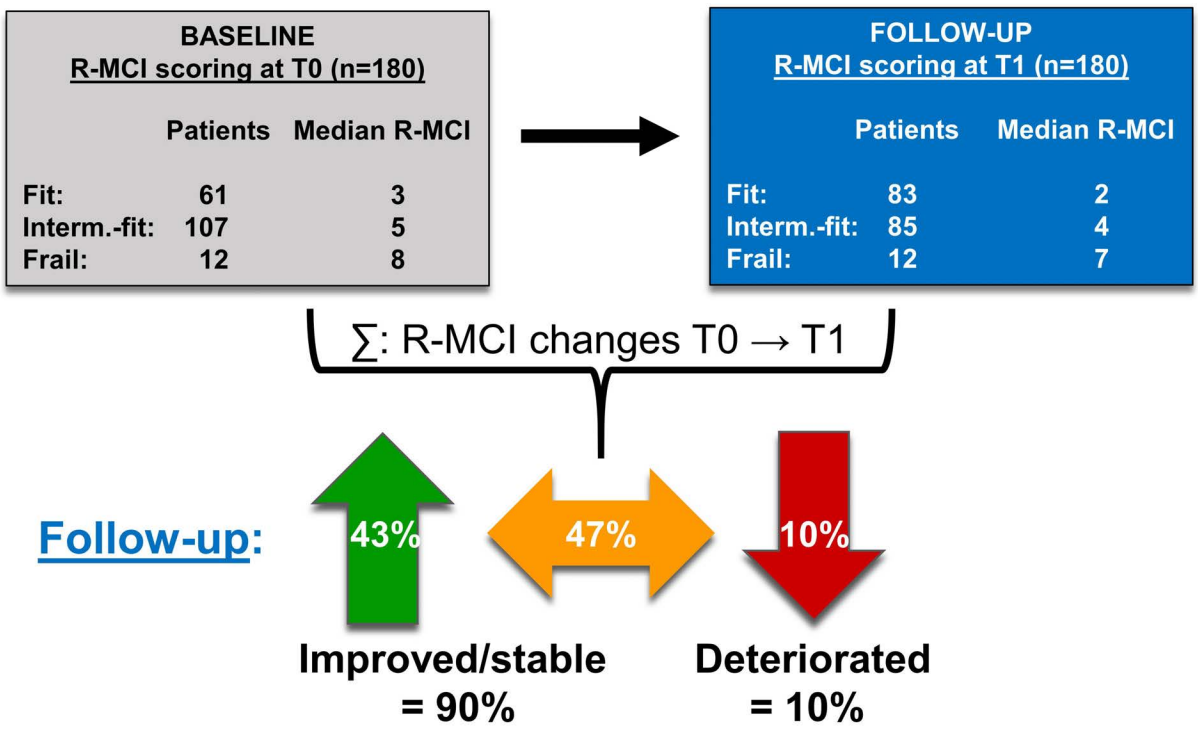

Figure 4. Changes in revised-myeloma comorbidity index scoring from start of induction (T0) to 6-24 months after first revised-myeloma comorbidity index assessment (T1) in 180 follow-up patients. R-MCI: revised-myeloma comorbidity index; Interm.-fit: intermediate-fit.

prior analyses, R-MCI subgroups differed much more than age or dose intensity subgroups, supporting the paradigm of an objective, functional GA and risk score.[5,8,39-42] Notably, ≥70 and 60-69-year-old (transplant-eligible) patients showed similar results regarding SAE, OS and PFS and thereby differed from <60-year-old patients, whereas for fitness groups, fit and intermediate-fit patients were comparable and very distinct from frail patients. Since patients ≥70 years are often excluded from clinical trials and more intensive therapies, we assessed this age group more thoroughly.[6,34,42,43] Of interest, 32% of our ≥70-year-old patients received a SCT after physicians' appraisal (Table 2). Nevertheless, 56% (n=28) of patients ≥70 years, who did not receive a SCT, were classified as either intermediate-fit or fit. Thus, those patients could have received intensive treatment. Larocca *et al*. elegantly demonstrated the benefit of a therapy-decision approach (dose-adjusted Rd-R *vs*. continuous Rd) via IMWG-frailty index in intermediate-fit patients in a prospective study.[20] An ongoing, equally important Medical Research Councils study randomizes unaltered to adjusted treatment according to fitness results (FiTNEss study, *clinicaltrails gov. Identifier: NCT03720041*, PI: G.Cook), both supporting our findings.

Concerning patients' outcome, we observed a substantial OS and PFS advantage in fit and intermediate-fit *versus* frail patients (Figure 2A and B). In line, Facon *et al*. propagated a simpler approach of the IMWG-frailty score, dividing patients likewise into non-frail *versus* frail patients, which seems straightforward for clinical routine and clinical trials.[21] An understandable request is that these risk-assessments should not be time-consuming and prospectively performed.[7] Both, the R-MCI and IMWG-frailty index offer online tools for their automatic calculation.

Strengths of our analysis were the meticulous examination of a NDMM patient cohort, of performed treatment, doses, SAE, PFS and OS in R-MCI, age and therapy intensity subgroups. Moreover, 72% of the initially assessed patients could be included in our follow-up analysis and their constitution and fitness, as measured via R-MCI, revealed improvement or stabilization in 90% and deterioration in only 10%. We have previously described in an even more detailed functional analysis using 12 different comorbidity scores and functional tests: the assessments more frequently and significantly changed in younger patients (<70 years) and those with good response (≥PR), suggesting a better functional reconstitution in younger and responsive than in older and less responsive myeloma patients.[8] These 10% of patients, whose R-MCI deteriorated in our follow-up analysis, should be reliably identified, because fittingly chosen therapies are relevant to perform and will ideally improve patients' quality of life (QoL).[8] This was also reflected in frequencies of non-hematological SAE, which were much lower in patients with improved or stable R-MCI (both 0.39/per patient) than in those with deteriorated R-MCI (0.53/per patient). No difference in infections was observed, most likely, due to the use of detailed chemotherapy treatment plans, including strict antibiotic prophylaxis schedules therein.[24] Although OS differences between these subgroups were hampered by limited patient numbers with deteriorated R-MCI, our follow-up analysis confirmed that MM treatment may indeed improve patients' constitution. Renal impairment and/or frailty (including KPS) may recover under MM therapies, whereas in those not improving and deteriorating with QoL domains, therapeutic adjustments are important to consider.[8] Additionally, our median observation period of 5.4 years was substantial, therefore our Kaplan-Meier results in all patients, in R-MCI, age, SAE-experiencing and dose-reduced patients were robust and mature. So far, there are few studies on prospective MM-specific risk tools for therapy-decision-support for NDMM and even lesser for relapsed/refractory (RR)MM patients, albeit these data and currently ongoing GIMEMA, MRC, HOVON and other studies support these endeavors.[44-46] Lastly, these data impressively confirm that the R-MCI seems superior to age-based treatment pathways.

Limitations of our study were the single institution approach, yet due to strict inclusion criteria regarding patients' and therapy data, all patients included provided infinitely detailed information. Another criticism could be the heterogeneity in patients (age range, 27-92 years), with a considerable number of patients <70 years (71%), as is typical for tertiary centers in Germany (*vs*. more centralized institutions and countries). Since our university and catchment area-treated patient population was relatively young and the majority received ASCT, we refrained from non-ASCT *versus* ASCT-based subgroup analyses, but considered all patients as one group. Besides, one could criticize the use of other than VCD-induction protocols in rare subgroups. Underlying AL-amyloidosis could also been argued to be possibly excluded, which we decided against, because all patients were initially diagnosed with MM only, but determined with AL amyloidosis by us, thus initially remaining undetected.[38] Lastly, we did not analyze the event-free survival as shown in prior studies,[20] as we focused on OS/PFS. The former will be part of another upcoming study at our institution.

In conclusion, our results demonstrate the higher frequency of SAE, higher discontinuation rates and early mortality in frail patients, supporting MM patients' need for individualized induction and relapse protocols.[17,23,46,47] Full-dose intensity for fit and reduced doses for frail patients appears pertinent, whereas intermediate-fit patients need continuing consideration. The precise fitness assessment in MM, similar to other hematological malignancies, seems relevant to achieve favorable treatment results, less DR, SAE, as few unscheduled re-hospitaliza-

tions and preserved QoL.[7,12,42,48,49] The latter demonstrated itself to be possible even after intensive regimens, after allogeneic transplantation or quadruplet RRMM treatment.[8,17,23,27,28] The implementation of functional assessments in myeloma TB may also support physicians in treatment decisions, since this adds an objective assessment of patients' individual constitution and possible treatment endurance. Future studies are needed to evaluate the benefits of a functionally adapted treatment approach *versus* ´treatment as usual´. Prospective studies using the R-MCI in TB for therapeutic decision support are in process at our CCCF.

Disclosures

No conflicts of interest to disclose.

Contributions

MH, ME, and all other authors performed the analysis. MH, GI, HR and ME analyzed results. MH, GI and ME prepared tables and figures. ME, RW, GI designed the research and MH and ME wrote the paper. All authors approved and carefully revised the paper.

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Data-sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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