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Dynamic frailty-tailored therapy (DynaFiT): A proof-of-concept study in elderly patients with newly diagnosed multiple myeloma

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Emerging evidence indicates that the fitness/frailty status of elderly patients with multiple myeloma (MM) is highly dynamic, influenced by factors such as aging, disease progression, and treatment. This underscores the importance of basing therapeutic decisions not only on initial fitness/frailty assessments but also on their changes over the course of treatment. In this regard, Zhang et al[1] have recently reported, to our knowledge, the first prospective study on an individualized dynamic frailty-tailored therapy (DynaFiT) for elderly patients with newly diagnosed MM (NDMM), who exhibit various fitness/frailty statuses.

MM is a hematologic malignancy primarily affecting older adults. The median age at diagnosis is 69 years, with approximately one-third >75 years and ~10% >85 years. Estimates suggest an 80% increase by 2030 in the diagnosis of MM among patients >65 years. Although the advent of novel agents and therapies over the past two decades has significantly improved outcomes for MM patients, older patients have experienced less benefit. This reduced efficacy is primarily due to their inability to tolerate aggressive frontline therapies and their ineligibility for transplantation. The older MM patient population is heterogeneous with varying degrees of fitness/frailty. Fit patients may withstand intensive therapies well and benefit from them, but frail patients are more prone to treatment-related toxicities, often leading to treatment discontinuation (TD) and poorer outcomes. Thus, accurately determining a patient's fitness/frailty status is crucial for treatment decision-making that optimally balances efficacy and safety for this vulnerable population. Consequently, geriatric assessments have been integrated into multiple clinical trials, especially for transplant-ineligible or specifically frail and intermediate-fit patients, where fitness/frailty is typically assessed at diagnosis.[2–6]

To identify prospective clinical studies focused on frailty-tailored therapy in MM published in English, a comprehensive literature search was conducted through PubMed in February 2024 using the terms "multiple myeloma" and "frail." This search yielded 272 articles. Among these, only one study, known as FitNEss—an ongoing randomized phase III trial with registration numbers ISRCTN17973108 and NCT03720041—aims to determine if prospective dose adjustments based on patient frailty can improve patients' ability to continue therapy, reduce toxicity, and enhance outcomes in transplant-ineligible patients with NDMM. According to the study protocol,[7] participants will be randomized (1:1) into two arms for both induction (R1) and maintenance (R2) phases. During R1, all participants will undergo up to 12 cycles (28 days each) of induction therapy using ixazomib (I), lenalidomide (R), and dexamethasone (d), with standard up-front dosing followed by toxicity-dependent dose modifications in the reactive arm, or frailty score-adjusted up-front dose reductions in the adaptive arm. In the adaptive arm, doses will be adjusted according to changes in frailty category (as per the revised International Myeloma Working Group frailty index/IMWG-FI and UKMRA Myeloma Risk Profile/MRP) at the start of cycles 3, 5, and 7, with possible dose escalations for suboptimal responders under specific criteria. Participants who remain alive and progression-free after 12 induction cycles will be re-randomized to receive either lenalidomide plus ixazomib or lenalidomide plus placebo as maintenance therapy. The primary outcome for R1 is the rate of early treatment cessation (reactive arm vs adaptive dosing arm) in participants categorized as "unfit" or "frail" at baseline, while for R2, it is progression-free survival (PFS). Dynamic changes in the frailty category during treatment were presented at the 65th ASH annual meeting, with randomization of 29% fit, 32% unfit, and 39% frail patients as per the IMWG-FI at baseline. Notably, 15% of frail and 16% of unfit patients showed improvement at any timepoint, whereas deterioration was seen in 27% of unfit and 21% of fit patients. Patients who improved experienced fewer treatment-related safety events (26%) compared to those who deteriorated (59%) or remained stable (34%). The final impact of this frailty-tailored therapeutic approach on participant outcomes remains to be determined.

Three prospective studies have been designed specifically for frail and intermediate-fit patients with NDMM. The HOVON-143 trial (phase II) is the first study to target frail patients, defined by the IMWG-FI.[4] Participants in this trial received nine 28-day induction cycles of ixazomib-daratumumab-low-dose-dexamethasone (Ixa-Dara-dex), followed by maintenance therapy with ixazomib and daratumumab. The primary endpoint was the overall response rate (ORR) during induction. Despite

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liberal exclusion criteria, which included very frail patients, the ORR was 78% (8% ≥complete response [CR], 28% very good partial response [VGPR], and 43% partial response [PR]), with a median PFS of 13.8 months and a 12-month overall survival (OS) of 78%. However, 51% of participants discontinued induction therapy prematurely: 19% due to progressive disease (PD), 9% due to toxicity, 9% due to intercurrent death, and 6% due to noncompliance; cumulative grade ≥3 hematologic and nonhematologic toxicity was reported in 31% and 74% of patients, respectively. Consequently, while treatment with Ixa-Dara-dex results in a rapid and high response rate, TD due to toxicity and early mortality remains a concern in this very frail population. Notably, outcomes vary significantly among frail subpopulations, with much better results observed in patients defined solely by age (>80 years) than those categorized by age (≤80 or >80 years) with additional frailty factors. The HOVON-143 trial also included intermediate-fit patients,[5] who achieved an ORR of 71% during induction and 72% during maintenance (2% ≥CR, 35% VGPR, and 34% PR during induction; 12% ≥CR, 31% VGPR, and 29% PR during maintenance), with a median PFS of 18.2 months and a 3-year OS of 83%. 77% of these patients had TD, primarily due to PD (49%), followed by toxicity (9%), noncompliance (8%), and sudden death (3%). Additionally, 46% of patients did not proceed to maintenance, with 63% halted by PD, 13% by toxicity, 10% by noncompliance, and 3% by sudden death; cumulative grade ≥3 hematologic and nonhematologic toxicity was reported in 12% and 51% of patients, respectively. Clinically meaningful improvements in quality of life were observed in both frail and intermediate-fit groups. Interestingly, while all participants received the same treatment, intermediate-fit patients had a relatively lower ORR and a higher rate of TD due to PD compared to frail patients, suggesting suboptimal treatment intensity for this group and challenging the "one-size-fits-all" approach for older patients with varying fitness/frailty statuses. Dynamic changes in frailty scores were also noted in the HOVON-143 trial (presented at the 65th ASH annual meeting): of the 29 frail patients who could improve, 17% became intermediate-fit and 3% became fit; of the 39 intermediate-fit patients that could improve, 15% became fit and 13% became frail. Improvement in frailty scores was associated with prolonged survival of frail and intermediate-fit patients.

In another study for frail patients (defined by the IMWG-FI or Mayo frailty index) with NDMM,[8] participants received six to eight cycles of induction therapy with ixazomib, lenalidomide or pegylated liposomal doxorubicin (D), and dexamethasone (IRd or IDd). The primary endpoint was the ORR across the different induction regimens. The ORR was 82% (25% ≥CR, 37% VGPR, and 12% PR) for the IRd group and 77% (12% ≥CR, 40% VGPR, and 25% PR) for the IDd group, with median PFS of 21.6 and 13.9 months, and median OS not reached and of 29.2 months, respectively. TD during induction occurred in 47% of patients in the IRd group (25% due to relapsed/refractory disease, 12% due to toxicity, 8% due to noncompliance, and 2% due to infection-related death) and in 55% of patients in the IDd group (22% due to relapse, 12% due to toxicity, 9% due to noncompliance, and 7% due to infection-related death). Cumulative grade ≥3 hematologic adverse events (AEs) were reported in 17% and 22% of patients, and grade ≥3 nonhematologic AEs in 23% and 35% of patients in the IRd and IDd groups, respectively. Interestingly, the ORR and TD during induction for the IRd group are comparable to those observed in frail patients treated with Ixa-Dara-dex in the HOVON-143 trial.

The first study for intermediate-fit patients with NDMM, also defined by the IMWG-FI, investigates dose/schedule-adjusted lenalidomide-dexamethasone (Rd) therapy in this population.[6] Participants received nine cycles of induction with standard Rd therapy, followed by maintenance with a reduced dose of lenalidomide without dexamethasone (Rd-R) versus continuous Rd. The primary endpoint was event-free survival (EFS), defined as the occurrence of grade 4 hematologic AEs, grade 3 to 4 nonhematologic AEs, discontinuation of lenalidomide, PD, or death. The EFS was 10.4 versus 6.9 months for Rd-R and continuous Rd, respectively, with an ORR of 78% (5% ≥CR, 28% VGPR, and 27% PR) versus 68% (1% ≥CR, 22% VGPR, and 30% PR), median PFS of 20.2 versus 18.3 months, and a 3-year OS of 74% versus 63%. Discontinuation of lenalidomide occurred in 24% versus 30%, and discontinuation of dexamethasone in 14% versus 34% of patients on Rd-R and continuous Rd, respectively. At least one grade ≥3 hematologic AE was reported in 26% versus 20% of patients, and at least one grade ≥3 nonhematologic toxicity was reported in 33% versus 43% of patients. Overall, 19% deaths not related to PD occurred (17% in the Rd-R group and 23% in the continuous Rd group), mainly due to AEs (predominantly infections).

Additionally, post-hoc subgroup analyses for frail and intermediate-fit patients with NDMM were retrospectively performed in two studies of transplant-ineligible patients: the ALCYONE trial, which compared bortezomib (V), melphalan (M), and prednisone (P; VMP) versus Dara-VMP, and the MAIA trial, which compared Rd versus Dara-Rd.[2,3] However, the frailty category in these studies was defined by the S-FI, based on age, CCI, and baseline ECOG PS, rather than by the IMWG-FI, which is currently considered the gold standard for geriatric assessment in MM. Consequently, the results from these analyses cannot be directly compared with those from studies using the IMWG-FI for frailty categorization. In another subgroup analysis, frail patients (also defined by the S-FI) who had previously been treated with lenalidomide in the OPTIMISMM trial were evaluated for the efficacy and safety of pomalidomide (P), bortezomib (V), and dexamethasone (d; PVd) versus Vd.[9] However, this trial targets patients with relapsed/refractory MM, rather than NDMM.

Thus far, in virtually all clinical studies for elderly (transplant-ineligible) patients published (except the ongoing FiTNess trial), treatment intensity is tailored according to the baseline fitness/frailty status, while dose modifications (typically reductions) during treatment are primarily due to toxicity (Table 1). The prospective study conducted by Zhang et al[1] has demonstrated the feasibility and potential benefits of a predesigned therapy (DynaFiT), where treatment intensity is tailored not only to the baseline frailty category but also to dynamic changes in the frailty category assessed at the start of each induction cycle. This approach appears particularly beneficial for elderly patients (≥65 years) in real-life clinical settings.[1] The therapy utilizes a regimen of bortezomib, lenalidomide, dexamethasone (VRd), adjusting the intensity of all three agents—either escalating doses with an improvement or de-escalating with a deterioration—based on longitudinal changes in the frailty category (defined by the IMWG-FI) at the start of each of the eight cycles. During induction, 58% of frail patients improved their fitness status and thus had their treatment intensity increased, whereas 20% of fit patients had their treatment intensity reduced due to deterioration. The ORR was 100% (≥VGPR 87%), 93% (86%), and 73% (57%) for fit, intermediate-fit, and frail patients, respectively, with 12-month PFS rates of 85%, 75%, and 46%, and 12-month OS rates of 90%, 75%, and 54%. The TD rate was 30%, 25%, and 49% for fit, intermediate-fit, and frail patients, mainly due to AEs (predominantly infections), rather than PD, particularly in frail patients. Three (3%) patients (one intermediate-fit and two frail) died, all within the first two cycles. Notably, frail patients who received induction therapy supplemented with daratumumab, an anti-CD38 monoclonal antibody with a favorable safety profile approved for transplant-ineligible NDMM,[10] exhibited a low TD rate.

In summary, despite rapid advances in the treatment of MM, managing elderly patients with varying fitness/frailty statuses remains a significant challenge. Currently, treatment intensity for elderly patients is typically determined based on their baseline fitness/frailty status, although it may be reduced due to

Table 1

Prospective studies of pre-designed frailty-tailored therapies in patients with newly diagnosed multiple myeloma.

	HOVON-143		Bao's	Larocca's	FitNEss	DynaFiT		
Participants	Frail*	Inter-fit*	Frail†	Inter-fit*	TI‡	Frail*	Inter-fit*	Fit*
Induction	Ixa-Dara-dex		IRd vs IDd	Rd	IRd		VRd (Dara)§	
Dose adjustment	Due to AEs (dose reduction)				According to frailty category changes			
Time of adjustment	Whenever the regimen is not tolerated				c3, 5, 7	Each of 8 cycles		
Maintenance	Ixa-Dara		Id	R vs Rd	IR vs R	Rd (Dara)§		
Improvement‖	20%	15%	NA	NA	15% (frail) 16% (unfit)	58%	13%	–
Deterioration‖	–	13%	NA	NA	21% (fit) 27% (unfit)	–	13%	20%
ORR	78%	71%	82% vs 77%	78% vs 68%	NA	73%	93%	100%
sCR or CR, %	8	2	25 vs 12	5 vs 1	NA	43	64	60
VGPR, %	28	35	37 vs 40	28 vs 22	NA	13	21	27
PFS	13.8 mo (median)	18.2 mo (median)	21.6 vs 13.9 mo (median)	20.2 vs 18.3 mo (median)	NA	46% (1 y)	75% (1 y)	85% (1 y)
OS	78% (1 y)	83% (3 y)	NR vs 29.2 mo (median)	74% vs 63% (3 y)	NA	54% (1 y)	75% (1 y)	90% (1 y)
TD	51%	77%	47% vs 55%	24% vs 30% (R) 14% vs 34% (d)	NA	49%	25%	30%
Top reason for TD	PD	PD	PD	PD	NA	AE	AE PD	AE
Non-hem AE (G ≥3)	74%	51%	23% vs 35%	33% vs 43%	NA	27%	6%	15%
Hem AE (G ≥3)	31%	12%	17% vs 22%	26% vs 20%	NA	2%	0%	0%
Reference #	4	5	8	6	7		1	

AE = adverse event, c = cycle, CR = complete response, D = pegylated liposomal doxorubincin, Dara = daratumumab, dex or d = dexamethasone, G = CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) grade, Inter-fit = intermediate-fit, Ixa or I = ixazomib, NA = not available, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, R = lenalidomide, sCR = stringent complete response, TD = treatment discontinuation, TI = transplant-ineligible, PD = progressive disease, V = bortezomib, VGPR = very good partial response.

*The frailty category is defined by the IMWG (International Myeloma Working Group) frailty index (FI).

†Frail patients are defined by either the IMWG-FI or Mayo frailty index.

‡The frailty category is defined by the revised IMWG-FI and MRP (UKMRA Myeloma Risk Profile).

§Daratumumab is recommended for frail patients.

‖Changes in the frailty category during induction.

treatment-related toxicity. However, since fitness/frailty status can change over time, decisions made based solely on baseline assessments may become less effective for frail patients who improve in fitness or potentially harmful for fit patients who later decline during the treatment course. The individualized DynaFiT approach allows for timely adjustments to balance safety and efficacy throughout the treatment process, aiming to maximize efficacy while minimizing toxicity. This approach helps to prevent undertreatment in fit and intermediate-fit patients, and overtreatment in frail patients, making it a potentially valuable strategy for managing this diverse and vulnerable population in everyday clinical practice.

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AUTHOR CONTRIBUTIONS

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