Journal of Hematology & Oncology

CORRESPONDENCE

Open Access

Individualized dynamic frailty-tailored therapy (DynaFiT) in elderly patients with newly diagnosed multiple myeloma: a prospective study

Yingjie Zhang[1,2†], Xinyue Liang[1†], Weiling Xu[3], Xingcheng Yi[2], Rui Hu[1], Xintian Ma[1], Yurong Yan[1], Nan Zhang[1], Jingxuan Wang[1], Xiaoxiao Sun[1], Yufeng Zhu[1], Mengru Tian[1,2], Maozhuo Lan[2], Mengtuan Long[2], Yun Dai[2*] and Fengyan Jin[1*]

Abstract

It remains a substantial challenge to balance treatment efficacy and toxicity in geriatric patients with multiple myeloma (MM), primarily due to the dynamic nature of frailty. Here, we conducted a prospective study to evaluate the feasibility and benefits of dynamic frailty-tailored therapy (DynaFiT) in elderly patients. Patients with newly diagnosed MM (aged ≥ 65 years) received eight induction cycles of bortezomib, lenalidomide, and dexamethasone (daratumumab was recommended for frail patients), with treatment intensity adjusted according to longitudinal changes in the frailty category (IMWG-FI) at each cycle. Of 90 patients, 33 (37%), 16 (18%), and 41 (45%) were fit, intermediate fit, and frail at baseline, respectively. Of 75 patients who had geriatric assessment at least twice, 28 (37%) experienced frailty category changes at least once. At analysis, 15/26 (58%) frail patients improved (27% became fit and 31% became intermediate fit), 4/15 (27%) intermediate fit patients either improved or deteriorated (two for each), and 6/30 (20%) fit patients deteriorated. During induction, 34/90 (38%) patients discontinued treatment, including 10/33 (30%) fit, 4/16 (25%) intermediate fit, and 20/41 (49%) frail; 14/40 (35%) frail patients discontinued treatment within the first two cycles, mainly because of non-hematologic toxicity (mostly infections). For fit, intermediate-fit, and frail patients, the overall response rate was 100%, 93%, and 73%, respectively; one-year overall survival was 90%, 75%, and 54%, respectively. Therefore, the individualized DynaFiT is feasible and promising for heterogeneous elderly patients.

Keywords Frailty, Dynamics, Frailty-tailored therapy, Elderly, Multiple myeloma

†Yingjie Zhang and Xinyue Liang contributed equally to this work.

*Correspondence:
Yun Dai
daiyun@jlu.edu.cn
Fengyan Jin
fengyanjin@jlu.edu.cn

[1]Department of Hematology, First Hospital of Jilin University, 71 Xinmin Street, Changchun, Jilin 130012, China
[2]Laboratory of Cancer Precision Medicine, First Hospital of Jilin University, 519 Dongminzhu Street, Changchun, Jilin 130061, China
[3]Department of Radiology, First Hospital of Jilin University, Changchun, Jilin, China

To the editor

Despite a remarkable improvement in the outcome of patients with multiple myeloma (MM), the benefit is considerably less impressive for elderly patients [1, 2], mainly because of treatment discontinuation (TD) due to frailty [3–6]. While frailty shows dynamic [7, 8], it is challenging to treat elderly patients featured by longitudinal frailty changes. To this end, we conducted a prospective study to investigate the feasibility and benefits of an individualized dynamic frailty-tailored therapy (DynaFiT) in elderly patients with newly diagnosed MM (NDMM).

Table 1 Frailty category changes, therapeutic responses, and treatment discontinuation

	All, N (%)	Fit, N (%)	Intermediate fit, N (%)	Frail, N (%)
Frailty category change	**(N = 75)**	**(N = 30)**	**(N = 15)**	**(N = 30)**
At least once	28 (37.3)	8 (26.7)	5 (33.3)	15 (50.0)[a]
At analysis				
Improved	17 (22.7)	–	2 (13.3)	15 (50.0)
Deteriorated	8 (10.7)	6 (20.0)	2 (13.3)	–
Response	**(N = 74)**	**(N = 30)**	**(N = 14)**	**(N = 30)**
ORR	65 (87.8)	30 (100)	13 (92.9)	22 (73.3)
CR or sCR	40 (54.1)	18 (60.0)	9 (64.3)	13 (43.3)
VGPR	15 (20.3)	8 (26.7)	3 (21.4)	4 (13.3)
PR	10 (13.5)	4 (13.3)	1 (7.1)	5 (16.7)
MR	4 (5.4)	0 (0)	1 (7.1)	3 (10.0)
SD	5 (6.8)	0 (0)	0 (0)	5 (16.7)
Reason for TD	**(N = 90)**	**(N = 33)**	**(N = 16)**	**(N = 41)**
Non-hematologic AE, any	17 (18.9)	5 (15.2)	1 (6.3)	11 (26.8)
Grade 2				
PNP-P	2 (2.2)	2 (6.1)	–	–
Grade 3				
Pneumonia	1 (1.1)	–	–	1 (2.4)
Cerebral infarction	1 (1.1)	–	–	1 (2.4)
Grade 4				
Pneumonia	5 (5.6)	1 (3.0)	–	4 (9.8)
Sepsis	4 (4.4)	1 (3.0)	–	3 (7.3)
Acute heart failure	1 (1.1)	1 (3.0)	–	–
Intercurrent death				
Sudden death	2 (2.2)	–	1 (6.3)	1 (2.4)
Acute renal failure	1 (1.1)	–	–	1 (2.4)
Hematologic AE				
Thrombocytopenia	1 (1.1)	–	–	1 (2.4)[b]
Reason other than AE, any	16 (17.8)	5 (15.2)	3 (18.8)	8 (19.5)
Deteriorating condition	4 (4.4)	–	1 (6.3)	3 (7.3)
Disease progression	3 (3.3)	1 (3.0)	1 (6.3)	1 (2.4)
Noncompliance	6 (6.7)	2 (6.1)	1 (6.3)	3 (7.3)
COVID-19	3 (3.3)	2 (6.1)	–	1 (2.4)

Abbreviations: ORR, overall response rate; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response; MR, minimal response; SD, stable disease; PFS, progression-free survival; OS, overall response; TD, treatment discontinuation; AE, adverse event; PNP-P, peripheral neuropathy grade 2 with pain.

[a]Including four patients with age > 80 years.

[b]TD because of cerebral hemorrhage secondary to thrombocytopenia.

This study was designed based on real-life practice at our center, which enrolled patients aged ≥ 65 years with NDMM who were transplant-ineligible or had no intent for immediate transplant, with minimal exclusion criteria (see Supplementary Information for Methods in detail). According to the NCCN Guidelines Insights: Multiple Myeloma (version 1.2020), participants received eight 21-day cycles of bortezomib, lenalidomide, and dexamethasone (VRd) for induction, followed by maintenance with Rd. Based on the EMN recommendation [9], treatment intensity was adjusted according to longitudinal changes in the frailty category, defined by the IMWG-FI [10], at the start of each cycle (Fig. S1). Daratumumab was recommended for frail patients [3–5]. Antibiotic/antiviral prophylaxis was recommended according to the IMWG's consensus [11].

From August 2021 to September 2023, 105 patients were registered, of whom 15 were deemed ineligible (Fig. S2). The baseline characteristics of 90 eligible patients are summarized in Table S1, of whom 33 (37%), 16 (18%), and 41 (45%) were fit, intermediate fit, and frail (Table S2), and their baseline characteristics are compared in Table S3.

At analysis, 75 patients had frailty assessment at least twice, of whom 28 (37%) experienced a change in the frailty category at least once during induction (Table 1). Of 41 frail patients (Fig. 1a), 11 patients had only baseline frailty assessment and four were age > 80 years; of 26 analyzable patients, 15 (58%) became fit (27%) or intermediate fit (31%), because of increased IADL, ADL, or both scores; of 15 patients (including two aged ≥ 80 years) receiving daratumumab, eight (62%) had an improvement. Of 30 fit patients (Fig. 1b), six (20%) became intermediate fit or frail, due to reduced IADL, ADL and IADL (because of grade 2 peripheral neuropathy with pain), or ADL plus age turning > 75 years. Of 15 intermediate-fit patients (Fig. 1c), two (13%) became fit due to increased ADL or IADL, and two became frail due to reduced IADL or ADL and IADL. 36/90 (40%) patients proceeded to maintenance, with trajectories of the frailty category from baseline to maintenance initiation shown in Fig. 1d. Of 34 patients with ECOG 3 or 4, 11 (32%) had an improvement in the frailty score, and 7 (21%) were tolerated to protocol treatment (though no improvement in the frailty score), while 16 (47%) discontinued treatment due to AEs (10), deteriorating conditions (3), noncompliances (2), or COVID-19 (1).

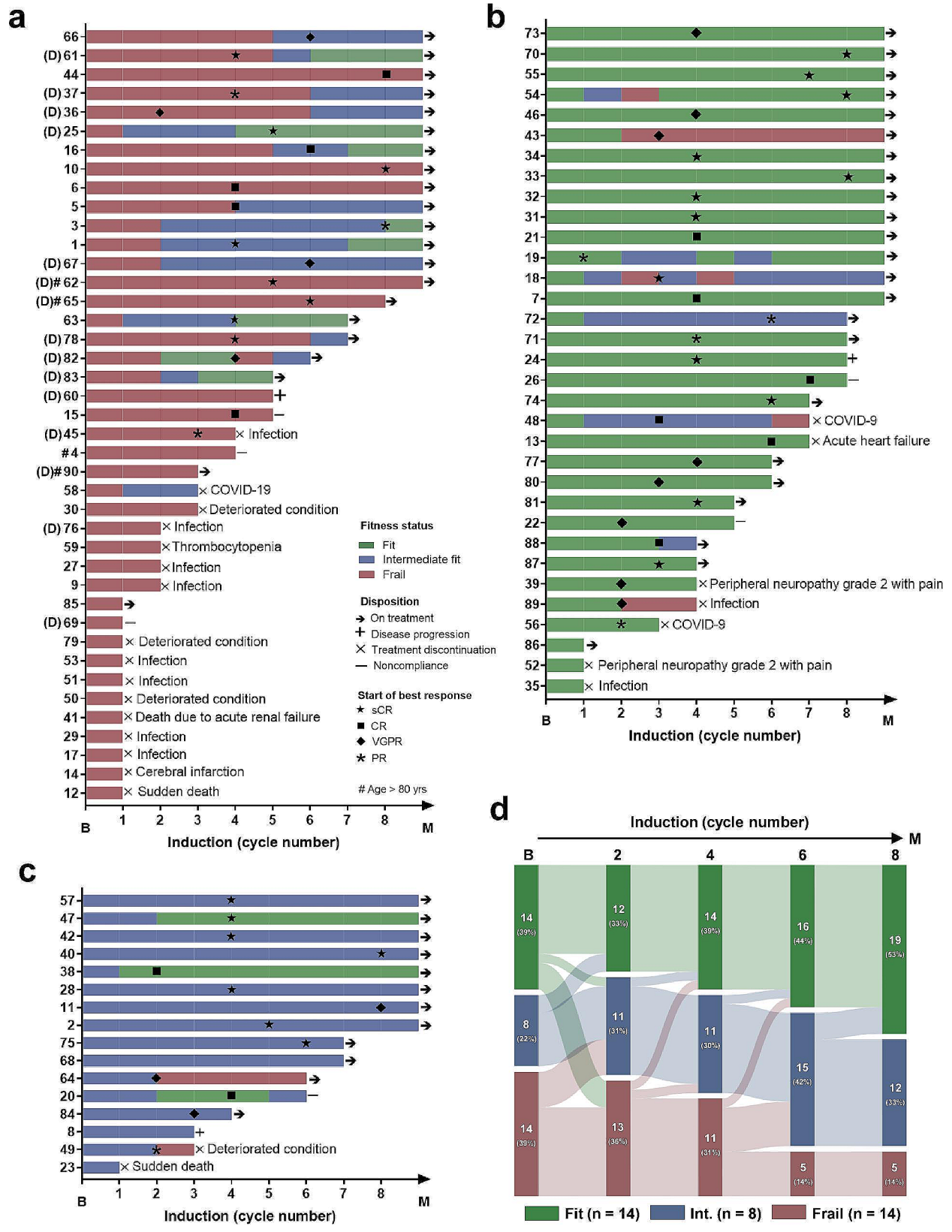

Fig. 1 Longitudinal changes of frailty. Changes in the frailty category during induction for patients who were defined as frail (**a**; patient #4 based on age > 80 years alone), fit **(b)**, and intermediate fit **(c)** at baseline, as well as who proceeded to maintenance **(d)**. B, baseline; M, maintenance; D, daratumumab; sCR, stringent complete response; CR, complete response; VGPR, very good partial response; PR, partial response

Of 74 patients evaluable for responses, the ORR was 88% (Table 1), including (s)CR (54%), VGPR (20%), and PR (14%). The ORR was 100%, 93%, and 73% for fit, intermediate-fit, and frail patients. Only one patient experienced progression during induction in each group. One-year PFS and OS were 85% and 90% for fit, 75% each for intermediate fit, and 46% and 54% for frail, respectively.

34/90 (38%) discontinued the protocol treatment, with 10/33 (30%), 4/16 (25%), and 20/41 (49%) for fit, intermediate fit, and frail, respectively (Table S4). The reasons for TD are described in Table 1, including five non-hematologic AEs, two noncompliances, two COVID-19s, and one PD for fit; intercurrent death, deteriorating condition, noncompliance, and PD (one for each) for intermediate fit; eleven non-hematologic AEs, three deteriorating conditions, three noncompliances, one cerebral hemorrhage secondary to thrombocytopenia, one PD, and one COVID-19 for frail. Of note, TD due to toxicity (mostly infections) accounted for 93% of frail patients who discontinued treatment within the first two cycles. Of 15 frail patients receiving additional daratumumab, only two (13%) discontinued treatment due to AEs.

Cumulative grade≥3 non-hematologic and hematologic toxicities were reported in 43 (48%) and 45 (50%) of 90 patients (Table S5). Cumulative grade≥3 non-hematologic toxicities were reported in 45% (15/33), 50% (8/16), and 49% (20/41) of fit, intermediate-fit, and frail patients, respectively (Table S6). Three patients (one intermediate fit and two frail) died during the first cycle (early mortality, 3.3%), with two sudden unexplained deaths and one due to acute renal failure.

In summary, we report for the first time, to our knowledge, that the DynaFiT is feasible for elderly patients in real-life practice. It allows timely adjusting of treatment intensity to balance efficacy and safety during treatment according to longitudinal changes in the frailty category to avoid both undertreatment and overtreatment in this heterogeneous population. While the choice of treatment in older patients based on the decision of the physician could be safe and effective [12], the DynaFiT may change the view of managing frail patients, to whom intensive therapy was generally not recommended [10]. Moreover, this study may also serve as a prototype for future studies to investigate other regimens in elderly patients with MM.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13045-024-01569-y.

Supplementary Material 1

Acknowledgements
We thank all participating clinicians and patients for their supports to this study.

Author contributions
F.J. and Y.D. conceived and designed the study; Y.Z., X.L., W.X., R.H., X.M., Y.Y., N.Z., J.W., X.S., Y.Z., M.T., and F.J. provided patients or collected data; Y.Z., X.L., X.Y., M.L.(1), M.L.(2), Y.D., and F.J. assembled data and performed statistical analysis; Y.Z., X.L., Y.D., and F.J. analyzed and interpreted data; Y.D. and F.J. wrote and edited the manuscript. All authors critically reviewed the manuscript and agreed to its submission for publication.

Funding
This work was supported by the National Natural Science Foundation of China (Grant # 81471165, 81670190, 81971108, 82370202, 81670189, 81870160, and 82270207), the Science and Technology Development Program of the Jilin Province (Grant # 20190201042JC, 20210509010RQ, 20190201163JC, and YDZJ202402002CXJD), and Interdisciplinary Integration and Innovation Project of Jilin University.

Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
The authors declare no competing interests.

Conflict of interest
All authors declare that they have no conflict of interest.

Ethical approval
The study was approved by the institutional review board (Approval # 21K048-002), and registered with the Chinese Clinical Trial Register (ChiCTR2100050220) and ClinicalTrials.gov (NCT06099912). The study was conducted in accordance with the Declaration of Helsinki and principles of good clinical practice. All patients provided written informed consent.

Received: 23 May 2024 / Accepted: 17 June 2024
Published online: 24 June 2024

References

1. Facon T, Leleu X, Manier S. How I treat multiple myeloma in geriatric patients. Blood. 2024;143:224–32. https://doi.org/10.1182/blood.2022017635.
2. Lee HC, Ailawadhi S, Gasparetto CJ, Jagannath S, Rifkin RM, Durie BGM, et al. Treatment patterns and outcomes in elderly patients with newly diagnosed multiple myeloma: results from the Connect® MM Registry. Blood Cancer J. 2021;11:134. https://doi.org/10.1038/s41408-021-00524-1.
3. Facon T, Cook G, Usmani SZ, Hulin C, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and dexamethasone in transplant-ineligible newly diagnosed multiple myeloma: frailty subgroup analysis of MAIA. Leukemia. 2022;36:1066–77. https://doi.org/10.1038/s41375-021-01488-8.
4. Mateos M-V, Dimopoulos MA, Cavo M, Suzuki K, Knop S, Doyen C, et al. Daratumumab plus Bortezomib, melphalan, and prednisone versus bortezomib, melphalan, and prednisone in transplant-ineligible newly diagnosed multiple myeloma: Frailty subgroup analysis of ALCYONE. Clin Lymphoma Myeloma Leuk. 2021;21:785–98. https://doi.org/10.1016/j.clml.2021.06.005.
5. Stege CAM, Nasserinejad K, van der Spek E, Bilgin YM, Kentos A, Sohne M, et al. Ixazomib, daratumumab, and low-dose dexamethasone in frail patients with newly diagnosed multiple myeloma: the Hovon 143 study. J Clin Oncol. 2021;39:2758–67. https://doi.org/10.1200/JCO.20.03143.
6. Groen K, Stege CAM, Nasserinejad K, de Heer K, van Kampen RJW, Leys RBL, et al. Ixazomib, daratumumab and low-dose dexamethasone in intermediate-fit patients with newly diagnosed multiple myeloma: an open-label phase 2 trial. EClinicalMedicine. 2023;63:102167. https://doi.org/10.1016/j.eclinm.2023.102167.
7. Cook G, Pawlyn C, Royle K-L, Senior ER, Everritt D, Bird J, et al. Dynamic frailty assessment in transplant non-eligible newly diagnosed myeloma patients: initial data from UK Myeloma Research Alliance (UK-MRA) Myeloma XIV

(FiTNEss): a frailty-adjusted therapy study. Blood. 2023;142:4748. https://doi.org/10.1182/blood-2023-188672.
8. Smits F, Groen K, Levin M-D, Stege C, Van Kampen RJW, Van Der Spek E, et al. Dynamic frailty status enables better prediction of survival probability - results of the HOVON 143 study. Blood. 2023;142:342. https://doi.org/10.1182/blood-2023-180006.
9. Larocca A, Dold SM, Zweegman S, Terpos E, Wäsch R, D'Agostino M, et al. Patient-centered practice in elderly myeloma patients: an overview and consensus from the European Myeloma Network (EMN). Leukemia. 2018;32:1697–712. https://doi.org/10.1038/s41375-018-0142-9.
10. Palumbo A, Bringhen S, Mateos M-V, Larocca A, Facon T, Kumar SK, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: an International Myeloma Working Group report. Blood. 2015;125:2068–74. https://doi.org/10.1182/blood-2014-12-615187.
11. Raje NS, Anaissie E, Kumar SK, Lonial S, Martin T, Gertz MA, et al. Consensus guidelines and recommendations for infection prevention in multiple myeloma: a report from the International Myeloma Working Group. Lancet Haematol. 2022;9:e143–61. https://doi.org/10.1016/S2352-3026(21)00283-0.
12. Tyczyńska A, Krzempek MK, Cortez AJ, Jurczyszyn A, Godlewska K, Ciepłuch H, et al. The real-world evidence on the fragility and its impact on the choice of treatment regimen in newly diagnosed patients with multiple myeloma over 75 years of age. Cancers (Basel). 2023;15:3469. https://doi.org/10.3390/cancers15133469.

Publisher's Note