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Impact of fitness categorization according to SIE/SIES/GITMO criteria in therapy-related and AML-MRC receiving CPX-351

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The full-text version of this article contains a data supplement.

Key Points

- Patients classified as fit according to SIE/SIES/GITMO score can achieve excellent long-term outcome upon CPX-351 administration.
- Disease genetic/cytogenetics predicted outcomes only in fit patients, whereas in unfit cases fitness level had greater prognostic impact.

CPX-351, a novel liposomal formulation of cytarabine and daunorubicin, represents the standard of care in fit patients with acute myeloid leukemia with myelodysplasia–related changes (AML-MRC) and therapy-related AML (t-AML). Considering its better safety profile than conventional intensive chemotherapy, we investigated its cost-to-benefit ratio, in terms of overall survival and of mortality, in a large multicentric series of AML-MRC and t-AML receiving CPX-351 outside clinical trials between 2019 and 2022. Patients were classified as fit or unfit for intensive chemotherapy through a comprehensive evaluation of age, comorbidities, and performance status by adopting Italian Society of Hematology/Italian Society of Experimental Hematology/Gruppo Italiano per il Trapianto di Midollo Osseo (SIE/SIES/GITMO) criteria. Disease risk was defined according to the European LeukemiaNet 2017 classification. Before treatment start, 328 of 403 (81.4%) patients were classified as fit and 75 of 403 (18.6%) as unfit. Three hundred and ninety-six had a full genetic/cytogenetic profile, with 17 (4%) being categorized as favorable risk, 162 (41%) intermediate risk, and 217 (55%) adverse risk according to European LeukemiaNet 2017. After induction, 230 of 403 (57.1%) patients achieved complete remission, with no differences between fit (57.3%) and unfit (56%) patients. However, the 2 groups significantly differed in terms of survival (median overall survival, 18 months vs 8 months for fit and unfit patients, respectively) and of 28- and 100-day mortality (4.6% vs 10.7% at 28 days and 14.3% vs 32% at 100 days for fit and unfit patients, respectively). In conclusion, the SIE/SIES/GITMO criteria distinguished patient subgroups with different short- and long-term outcomes after treatment with CPX-351. The update or design of dedicated fitness criteria could represent a future and valid strategy to optimize the use of this specific treatment.

Introduction

Within the spectrum of acute myeloid leukemia (AML), AML with myelodysplasia-related changes (AML-MRC) and therapy-related AML (t-AML) are characterized by distinctly adverse clinical outcomes.[1-4] A possible explanation is that they mainly affect older individuals, whose general conditions, burden of comorbidities, and past medical history frequently hamper the administration of therapies with curative intent.[4] Furthermore, unfavorable genetic features such as complex or monosomal karyotype and adverse molecular alterations are also common findings in this setting, influencing the probability of response to available treatments.[4,5] Overall, the combination of such unfavorable clinical and biological traits justifies the lack of response to conventional chemotherapy, with long-term remission rates of <20%.[6] In recent years, CPX-351, a novel liposomal formulation containing an optimal molar combination of cytarabine and daunorubicin, was granted approval for the treatment of patients with newly diagnosed t-AML and AML-MRC and currently represents the standard of care in fit patients with secondary AML.[7] Besides a documented superiority in terms of efficacy as compared with the classical "7+3" regimen,[7-9] there is also evidence that CPX-351 has a better safety profile than conventional intensive chemotherapy.[8,10,11] This raises the question of whether this compound might be better tolerated also in patients considered unfit and whether the clinical benefit is maintained in this category of patients. Among the available scores for fitness determination,[12-15] the SIE/SIES/GITMO criteria combine clinical parameters such as age, comorbidities, and performance status (PS) to classify patients into 3 groups: fit for intensive chemotherapy, unfit for intensive chemotherapy, and unfit for nonintensive approaches.[15] Although lacking a proper prospective validation, these criteria have been retrospectively evaluated in large cohorts of patients with intensively treated AML and are now commonly adopted both in clinical trials and in daily clinical practice.[15,16] However, these criteria have not been specifically tested in the subgroup of AML-MRC and t-AML, therefore we wanted to evaluate their applicability in a large series of patients diagnosed with these AMLs and who were homogeneously treated with CPX-351 in daily clinical practice.

Methods

This retrospective multicenter study included 403 adult patients (aged >18 years) with newly diagnosed nonpromyelocytic AML, whose diagnostic and therapeutic procedures were conducted at 36 Italian hematology institutions between 2019 and 2022. All patients were classified as having either AML-MRC or t-AML according to World Health Organization 2016 classification and received at least 1 induction cycle with CPX-351. Patients were categorized according to the European LeukemiaNet 2017 (ELN2017) classification into 3 risk groups: favorable (ELN2017-FR), intermediate (ELN2017-IR), and adverse (ELN2017-AR).[17] Fitness level was retrospectively attributed according to the SIE/SIES/GITMO criteria (Ferrara criteria), categorizing patients as fit or unfit for intensive chemotherapy. In detail, the complete list of operational criteria proposed by Ferrara et al was used to classify patients into Ferrara fit (F-fit; when no criteria met for unfitness for intensive chemotherapy) and Ferrara unfit (F-unfit; when ≥1 criteria met for unsuitability for intensive chemotherapy).[15] Detailed information on age, PS, cardiac, renal and hepatic function, and comorbidity burden in general was fully available for all patients.

Regarding pulmonary assessment, pulmonary functional testing was not performed in 81 of 403 (20.1%) cases. However, 20 of these patients already met another criterion for unfitness, whereas the remaining 61 patients were nonsmokers without known pulmonary comorbidities and with normal chest imaging studies and therefore unlikely to have abnormal pulmonary functional tests.[18] Treatment response was evaluated using the International Working Group 2003 criteria.[19] Complete remission (CR) was defined as the absence of leukemic blasts in the bone marrow (<5%), normal peripheral blood counts (neutrophils >1 × 10^3/μL and platelets >100 × 10^3/μL), and no signs of extramedullary disease.

The impact of the factors analyzed, as well as the prognostic relevance of the 2 classifications systems (clinical according to SIE/SIES/GITMO criteria and biological according to ELN2017), were evaluated through the established end points: CR rate, median overall survival (OS), and mortality at 28 and 100 days from first induction.

The protocol and related documents were approved by the ethics committee of the coordinating center on 6 March 2022 (approval no. 606/23/06/2022) and subsequently by each participating institution. The study was approved by the ethics committees of the participating institutions and was conducted in accordance with the Declaration of Helsinki. All participants gave their informed consent.

Statistical analysis

All analysis excluding landmark models were performed with IBM Statistical Package for the Social Sciences version 22 running on a Linux Environment. The R statistical package was used for landmark models and competing risk analysis.

Univariate analysis for CR probability and early mortality risk included age at diagnosis, AML subtype (AML-MRC vs t-AML), ELN2017 risk score, Ferrara criteria, and Eastern Cooperative Oncology Group (ECOG) score. The multivariate model for early mortality risk included age (as a continuous variable), ELN2017 risk score, ECOG score, and Ferrara criteria.

Dichotomous variables were compared using the χ^2 test or, as necessary, with the Fisher exact test. Continuous variables were compared with the Student *t* test or, if normal distribution could not be confirmed, with the Wilcoxon rank test. A linear regression analysis was performed for multivariate CR analysis.

Survival curves were built according to the Kaplan-Meier method, and univariate survival analysis was performed with the log-rank test. A Cox proportional hazards model was built for each multivariate survival analysis, including only variables that fulfilled the proportional risk criteria.

A 2-tailed *P* value of <.05 was considered statistically significant.

Results

General characteristics of study population

We identified a total of 403 patients with secondary AML, with a median age at diagnosis of 65 years (range, 32-79). Most of the patients (68.3%) were aged between 60 and 74 years, whereas the remaining 29.8% and 1.9% were aged between 18 and 60 years and ≥75 years, respectively. Male patients accounted for 56.1% of the entire cohort. At diagnosis, 194 of 403 (48.1%) patients had an ECOG PS of 0, 139 of 403 (34.5%) had PS of 1, 63 of 403 (15.6%) had PS of 2, and 7 of 403 (1.7%) had a PS of 3. Median number of preexisting comorbidities was 1 (range, 1-7). According to World Health Organization 2016 classification, 325 of 403 patients (80.6%) were classified as having AML-MRC, and 78 of 403 (19.4%) as having t-AML.

Based on the genetic/cytogenetic profile, 17 (4%) patients were categorized as ELN2017-FR, 162 (41%) as ELN2017-IR, and 217 (55%) as ELN2017-AR. Disease risk was not attributable in 7 (1.7%) patients due to incomplete genetic data. The retrospective application of the SIE/SIES/GITMO criteria resulted in 328 patients (81.4%) being classified as F-fit and 75 (18.6%) as F-unfit. Overall, the most frequent criteria leading to unfitness were age of ≥75 years (8 cases); ECOG PS of >2 (7 cases); severe cardiological, pulmonary, or hepatic comorbidities (10, 19, and 3 cases, respectively); and active infection resistant to anti-infective therapy (28 cases). The prevalence of F-unfit patients did not differ between the 2 groups of patients aged 18 to 59 and 60 to 74 years (18% and 19.6%, respectively).

Regarding the induction therapy, 336 (83.4%) patients underwent a single induction cycle and 67 (16.6%) underwent 2 induction cycles. Finally, 86 (21.3%) patients received a single consolidation cycle, 87 (21.6%) received 2 consolidation cycles, and 230 (57.1%) did not receive any consolidation cycle (Table 1).

Response to therapy according to fitness level and disease biology

After up to 2 induction cycles, 230 of 403 (57.1%) patients achieved a CR, with 206 of 403 (51.1%) patients achieving CR after the first induction course. No differences were observed in terms of CR when classifying the entire cohort according to AML subtype (CR of 57.2% vs 56.4% for patients belonging to the AML-MRC and t-AML groups, respectively; $P = .879$). As expected, the CR rate was proportional to disease risk according to ELN2017 (CR of 82.3% vs 69.1% vs 46.1% for ELN2017-FR, ELN2017-IR, and ELN2017-AR, respectively; $P < .01$). Conversely, no significant differences were observed in CR rates between F-fit and F-unfit patients (CR of 57.3% vs 56% for F-fit and F-unfit patients, respectively; $P = .944$). Superimposable CR rates were also confirmed after stratifying F-fit and F-unfit patients according to both AML subtype (eg, AML-MRC vs t-AML; $P = .796$) and disease risk ($P = .677$). However, we observed significantly different mortality rates after first induction between F-fit and F-unfit patients (4.6% vs 10.7% at 28 days and 14.3% vs 32% at 100 days for F-fit and F-unfit, respectively; $P < .0001$). The multivariate analysis confirmed the independent impact of fitness status according to Ferrara criteria on mortality at selected time points (28 days, 100 days, and overall; Table 2). Most frequent causes of death at 28 and 100 days from induction in F-fit patients were resistant disease (51%), infections (41%), or uncontrolled central nervous system bleeding (8%). In comparison, in F-unfit patients, the most frequent causes of early mortality were disease progression (38%) and infections (52%).

A total of 113 of 430 (28%) patients underwent hematopoietic stem cell transplant (HSCT): 106 of 328 (32.2%) F-fit and 7 of 75 (9.3%) F-unfit patients ($P < .05$; Table 3). Among the 7 F-unfit patients who eventually proceeded to HSCT, the criteria defining

Table 1. General characteristics of study population

Variable	Patients N = 403
Age at diagnosis, y (range)	65 (32-79)
Age groups, y, n (%)	
18-59	120 (29.8)
60-74	275 (68.3)
≥75	8 (1.9)
Sex (%)	
Female	177 (43.9)
Male	226 (56.1)
PS, n (%)	
0	194 (48.1)
1	139 (34.5)
2	63 (15.6)
3	7 (1.7)
AML subtype, n (%)	
AML-MRC	325 (80.6)
t-AML	78 (19.4)
ELN2017 risk, n (%)	
Favorable	17 (4.2)
Intermediate	162 (40.2)
Adverse	217 (53.8)
Not classifiable	7 (1.7)
SIE/SIES/GITMO, n (%)	
F-fit	328 (83.4)
F-unfit	75 (16.6)
Induction cycles, n (%)	
1	336 (81.4)
2	67 (18.6)
Consolidation cycles, n (%)	
0	230 (57.1)
1	86 (21.3)
2	87 (21.6)

unfitness at AML diagnosis were mainly the presence of active infection resistant to anti-infective therapy (n = 4), impaired cardiac function (n = 2), and ECOG PS of ≥2 (n = 1). All these conditions had resolved or significantly improved at the time of transplantation, allowing eligibility for the procedure.

Table 3. Correlation between CR rates and selected variables

Variable	General population	F-Fit	F-unfit
CR rate, n (%)	230/403 (57.1%)	188/328 (57.3%)	42/75 (56%)
CR according to AML subtype, n (%)			
AML-MRCf	186/325 (57.2)	154/271 (56.8)	32/54 (59.2)
t-AML	44/78 (56.4)	33/57 (57.9)	11/21 (52.4)
CR according to ELN2017, n (%)			
Favorable	14/17 (82.3)	10/12 (83.3)	4/5 (80)
Intermediate	112/162 (69.1)	90/132 (68.1)	22/30 (73.3)
Adverse	100/217 (46.1)	81/177 (45.7)	19/40 (47.5)
Not classifiable	4/7 (57.1)	4/7 (57.1)	0
HSCT, n (%)	113/403 (28)	106 (32.2)	7/75 (9.3)

Survival analyses

At a median follow-up of 10.1 months, the OS of the entire study cohort was 15 months (95% confidence interval [CI], 12.6-17.3). A significant survival difference was observed when comparing the 2 fitness groups. The median OS was 18 months (95% CI, 14.8-21.1) vs 8 months (95% CI, 4.1-11.8) for F-fit and F-unfit patients, respectively ($P < .001$; Figure 1).

When stratifying the study cohort by PS, median OS was of 18 months (95% CI, 14.7-21.2) for patients with ECOG PS of 0, 13 months (95% CI, 8.5-17.4) for patients with ECOG PS of 1, 11 months (95% CI, 7.2-14.7) for patients with ECOG PS of 2, and 4 months (95% CI, 0.1-11.7) for patients with ECOG PS of 3 ($P < .001$; supplemental Figure 1). No statistically significant differences were observed in terms of OS between the 2 groups of patients with AML-MRC and t-AML: median OS of 15 months (95% CI, 13.5-18.4) and of 11 months (95% CI, 6.6-15.3) for AML-MRC and t-AML, respectively ($P = .411$; supplemental Figure 2).

In the general population, median OS duration was consistent with ELN2017 risk category (median OS, not reached [NR] in the ELN2017-FR group, 19 months [95% CI, 16.1-21.9] in the ELN2017-IR group, and 12 months [95% CI, 8.8-15.1] in the ELN2017-AR group; $P = .002$; Figure 2).

We then further analyzed the 2 groups of F-fit and F-unfit patients based on disease risk according to ELN2017 criteria, aiming to evaluate the impact of the integrated combination of the 2 classification systems. In line with what was observed with CR rates,

Table 2. Multivariate Cox regression models for mortality from induction

	28-day mortality		100-day mortality		Overall mortality	
Characteristic	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Ferrara score	2.492 (1.015-6.114)	.025	2.814 (1.583-5.001)	<.001	2.202 (1.293-3.571)	.002
ELN2017	1.954 (1.233-4.976)	.057	0.984 (0.275-3.521)	.279	1.102 (0.351-3.461)	.091
ECOG PS	1.002 (0.330-3.040)	.451	0.967 (0.486-1.821)	.942	1.163 (0.706-1.927)	.274
Age	0.784 (0.323-1.900)	.586	1.012 (0.577-1.773)	.952	1.122 (0.627-2.001)	.493

HR, hazard ratio.

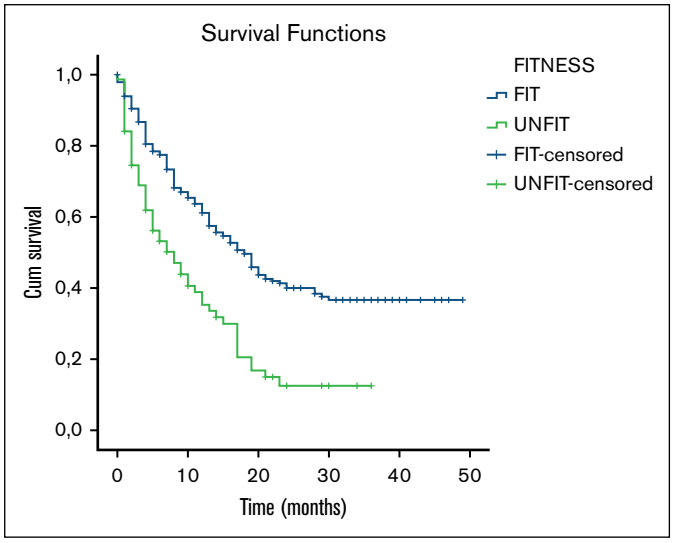

Figure 1. OS of the whole study population when stratified according to fitness level. Cum, cumulative.

OS of F-fit patients was proportional to disease risk (median OS, NR in the ELN2017-FR group; 20 months [95% CI, 17.1-22.8] in the ELN2017-IR group; and 13 months [95% CI, 9.3-16.6] in the ELN2017-AR group; $P = .002$; Figure 3A), whereas such a trend was not observed among F-unfit cases (median OS of 5 months [95% CI, 0.7-9.3] in the ELN2017-FR group, 11 months [95% CI, 2.6- 19.4] in the ELN2017-IR group, and 7 months [95% CI, 3.7-10.2] in the ELN2017-AR group; $P = .183$; Figure 3B).

Finally, we compared the impact of HSCT and consolidation therapy alone from the time of CR in the 2 groups of F-fit and F-unfit patients. In the group of patients not undergoing HSCT, the median OS was 21 months (95% CI, 17.5-24.5) in the F-fit group and of 13 months (95% CI, 8.5-17.5) in the F-unfit group ($P = .002$; Figure 4A). Among patients undergoing HSCT, we observed a particularly prolonged survival in F-fit patients (median OS, NR), compared with a median of 9 months (95% CI, 0.1-19.2) in the small subgroup of F-unfit patients undergoing the transplantation procedure (Figure 4B).

Discussion

In our experience, including a real-life cohort of 403 patients with AML-MRC or t-AML homogeneously treated with CPX-351, we observed a superimposable CR rate among fit and unfit subgroups. Nevertheless, the long-term outcomes of the 2 groups diverged, possibly due to the differences between the 2 groups in terms of mortality.

Secondary acute leukemias represent a group of AMLs with a particularly adverse prognosis, with significantly lower response rates to conventional chemotherapy compared with the de novo counterpart. This discrepancy cannot be attributed exclusively to the reduced susceptibility to standard treatment but depends on both the unfavorable biological characteristics of these subgroups and the peculiar clinical characteristics of these patients. In fact, factors such as advanced age, reduced PS, a high number of comorbidities, and previous clinical history (including type of previous neoplasm and/or treatment received) determine a low level of fitness in most of these patients. Consequently, administration of curative-intended treatments is feasible only in a small percentage of AML-MRC and t-AML cases.

After characterizing ~4 decades that lacked any new treatment alternatives, CPX-351 has been specifically approved for the treatment of patients with t-AML and AML-MRC who are considered eligible for intensive chemotherapy. This new agent, proven to be particularly effective in the treatment of secondary AMLs, currently represents the standard of care in fit patients affected by these disease subtypes. Furthermore, CPX-351 seems to be better tolerated than conventional treatments, probably because of its selective tropism for hematopoietic tissues, which could justify the lower extrahematological toxicities observed with respect to standard chemotherapy. For the purposes of fitness assessment, a fundamental prerequisite for the identification of the most appropriate therapeutic choice, several models are currently available.

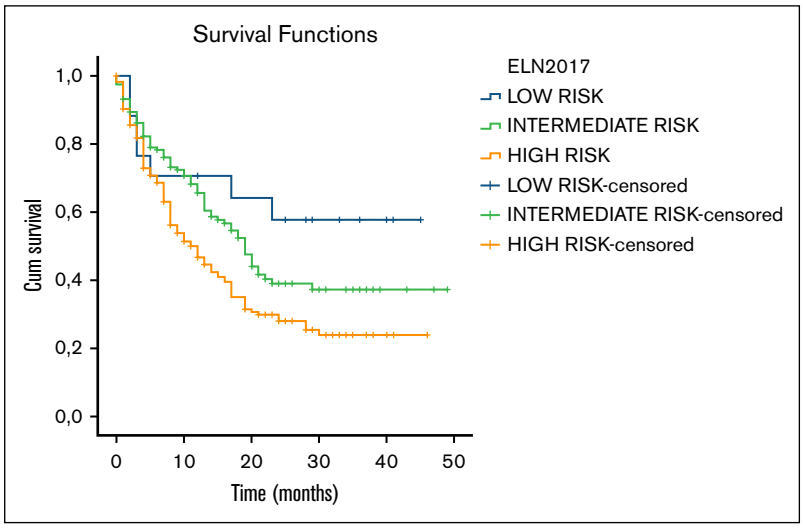

Figure 2. OS of the whole study population according to disease risk (ELN2017). Cum, cumulative.

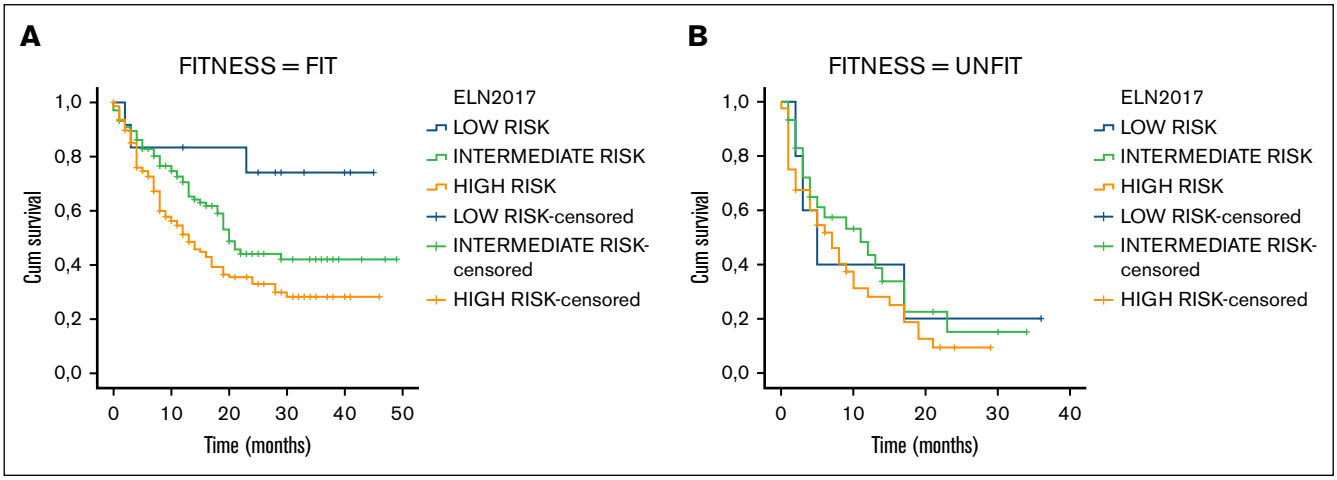

Figure 3. Impact of ELN2017 on OS. OS of (A) F-fit (328 patients) and of (B) F-unfit (75 patients) groups according to ELN2017 risk. Cum, cumulative.

The SIE/SIES/GITMO criteria, also called Ferrara criteria, summarize the efforts of a panel of experts in the treatment of AML and were designed with the aim of defining eligibility for the different intensities of treatment available. These criteria were retrospectively evaluated on a large cohort of patients with AML who were intensively treated, proving effective in predicting short-term mortality from induction, which was particularly high (42% at 100 days) among patients classified as unfit.[16] Nevertheless, in the absence of data on the efficacy and tolerability of CPX-351 in patients unfit to standard therapies, we aimed to compare the impact of this treatment in different fitness subgroups in terms of mortality and OS.

Through the retrospective application of the entire list of SIE/SIES/GITMO criteria, we identified 75 unfit patients, accounting for 18.6% of the entire study cohort. At the end of induction therapy, superimposable proportions of F-fit and F-unfit patients achieved CR. This overlap was maintained after stratifying the 2 subgroups with respect to single variables such as AML subtype (t-AML and AML-MRC) and disease risk according to ELN2017 criteria. However, we observed significantly different OS rates between the 2 groups. This discrepancy is likely to be attributable to the differences between the 2 groups in terms of mortality. These results are consistent with what has been observed in other studies supporting the utility of the SIE/SIES/GITMO criteria in identifying patients at higher risk of early mortality.[16] In particular, although the deaths of F-unfit patients were more likely attributable to nonleukemic causes at early time points, F-fit patients died more often from disease refractoriness later during follow-up. This underscores the need for refined fitness assessment, ideally incorporating multidimensional geriatric evaluation, which may help disentangle the relative contributions of fitness and disease biology to early mortality, as well as support appropriate therapeutic decision-making.[20] Conversely, we did not observe

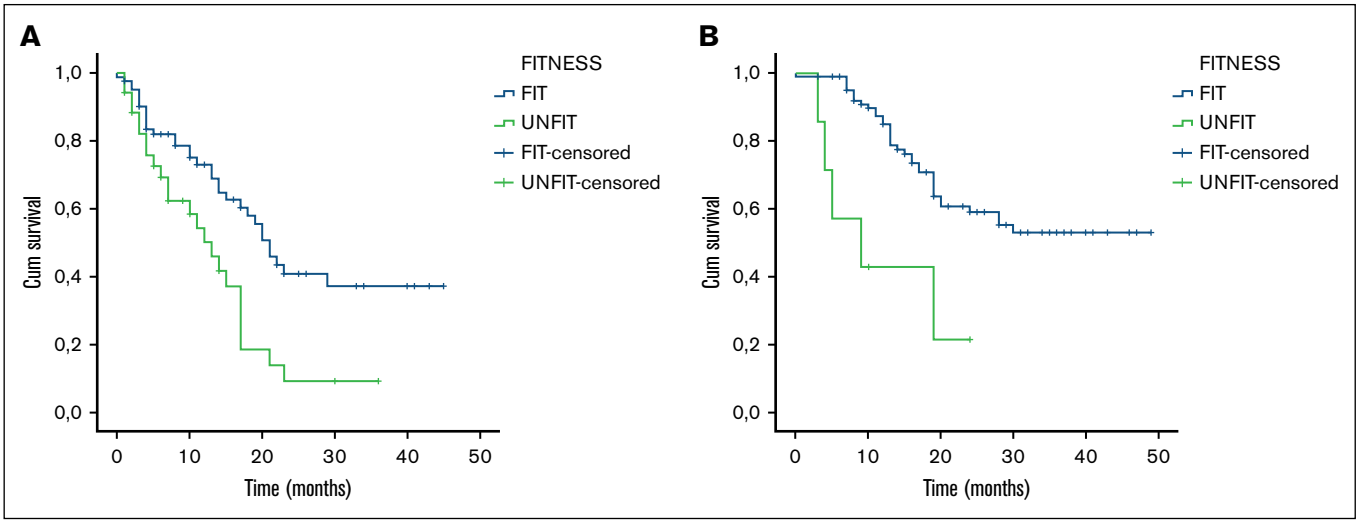

Figure 4. Impact of transplant on OS. OS of F-fit and of F-unfit patients (B) not receiving (117 patients) and (B) receiving HSCT (113 patients) once in CR. Cum, cumulative.

significant differences within the study cohort when stratifying the subgroups of fit and unfit patients with respect to single variables such as AML subtype (t-AML and AML-MRC).

In the subgroup of F-fit patients, we observed CR and global OS rates directly proportional to ELN2017 risk, as expected. In contrast, no clear stratification in terms of OS was observed in the subgroup of F-unfit patients when comparing the different ELN2017 categories. Although the limited size of the sample does not allow us to draw definitive conclusions, we can speculate that the biological characteristics of the disease play a secondary role in the prognostic stratification in this group, whose outcome is primarily defined by the level of fitness. Alternatively, and in line with new recommendations and evidence from recent studies,[21,22] we can hypothesize that ELN criteria perform better in a population of fit patients treated intensively, whereas unfit patients receiving less-intensive therapeutic approaches deserve specific biological profiling to help the clinical decision-making process.

Finally, we investigated the prognostic impact of HSCT compared with consolidation therapy alone after CR in the 2 groups of F-fit and F-unfit patients. For patients not undergoing HSCT, the clear distinction observed between F-fit and F-unfit patients in terms of OS reflects the results of the general series. Regarding patients undergoing HSCT, it is not possible to draw any firm conclusions on the role of the transplant in the context of F-unfit patients due to the small sample size (only 7 patients). Nevertheless, in the F-fit patient group, we observed particularly prolonged survival rates, with a median OS NR at the time of observation. These data underline the validity of the SIE/SIES/GITMO criteria in identifying patients who, once in remission, can benefit from a transplant procedure with promising chances of long-term survival.

In a future perspective, the update of the criteria for fitness definition could represent a useful strategy to improve the overall performance of this specific treatment, possibly expanding the proportion of patients with AML-MRC and t-AML who could benefit from the administration of CPX-351 with curative potential.

Authorship

Contribution: R.P. and F.G. conceptualized the research; R.P., F.G., P.M., A.V., and F.B. designed the study; R.P., F.G., L.F., F.F., P.M., M.P.M., P.C., M.R., S.C., C. Minotti, F.P., S.P., A. Corbingi, F.G., G.D.L., C.F., C.A., F. Mannelli, F. Lessi, F. Marchesi, L.B., D. Capelli, A.L.P., C.V., F.E.P., C. Mazzone, A.S., G.L., M.D., S.M., M.C., A.M., A.D.V., C.P., A.I., A.F., S.G., D. Cilloni, M.B., F. Lanza, M.G., R.C., A. Candoni, L.P., and E.T. enrolled patients; R.P., F.G., and P.M. analyzed data; R.P., F.G., P.M., C.R., R.M.L., A.V., and F.B. prepared the first draft of the manuscript; R.P., A.V., F.B., F. Moretti, and E.M. revised the manuscript; and all authors approved the final version of the manuscript.

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