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Geriatric Assessment in Older Patients with Acute Myeloid Leukemia: A Retrospective Study of Associated Treatment and Outcomes

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Abstract

We explored whether geriatric assessment variables predicted mortality in addition to known prognostic factors in 101 patients aged ≥65 with newly diagnosed AML. Baseline comorbidity score (HR=1.92; 95%CI 1.18–3.11), difficulty with strenuous activity (HR=2.18; 95%CI 1.19–4.00), and pain (HR=2.17; 95%CI 1.19–3.97) were independent prognostic factors for greater risk of death in a multivariable model that included cytogenetic risk group. They remained independent predictors in the subset of patients with baseline ECOG PS 0–1. Our results support the use of geriatric assessment to better predict prognosis in older patients with AML, even among those with excellent functional status.

Keywords

Geriatric Assessment; Leukemia; Acute; Myeloid; Prognosis; Performance Status; Comorbidity

Introduction

Acute myeloid leukemia (AML) is a disease of older adults whose incidence will increase dramatically in coming decades due to population aging.[1] AML patients over age 65 have much worse prognosis than younger patients, with a five-year disease-specific survival of

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only 5%.[2] These poor outcomes are due to a combination of age-related changes in disease biology and clinical factors such as decreased physiologic reserve, functional impairment and frailty.[3–5] Previous work has identified age, performance status, comorbidity, and cytogenetic risk group as important prognostic factors in older patients with AML.[6] However, few studies have explored the relationship between geriatric assessment and AML outcomes.

Comprehensive geriatric assessment (CGA) is a systematic method of identifying multiple predictors of morbidity and mortality in older adults that may impact cancer treatment and is recommended for older cancer patients by NCCN guidelines.[7] This recommendation was in part based on a multicenter study demonstrating that a self-administered geriatric assessment identified important prognostic factors in cancer patients.[8] A geriatric evaluation includes assessment of multiple domains including comorbidity and physical, cognitive and social function. The feasibility of performing a modified CGA in older patients with AML has been demonstrated, but it is not yet known how this information predicts outcomes.[9]

Careful assessment of the potential benefits and risks of therapy is particularly vital in AML, as intensive chemotherapy with cytarabine and an anthracycline is the only treatment that gives hope of long-term survival. Response to induction is poor among older adults and toxicity is substantially higher than in younger individuals, but selected patients can achieve remission and cure.[10–12] Patients who are not candidates for induction may benefit from non-intensive treatments such as hypomethylating agents, and some are best served by purely palliative approaches.[13, 14] However, it can be difficult to predict which older patients will benefit from chemotherapy using routine clinical and biological factors alone. Growing evidence suggests that measures of comorbidity and functional status may also be valuable prognostic factors in elderly patients with AML.[15–18] We utilized prospectively collected quality of life data to evaluate the utility of geriatric factors as predictors of survival in older patients with AML across varying treatment intensities.

Methods

Data Collection

We performed a retrospective cohort study of consecutive patients ≥65 years of age that presented to Dana-Farber Cancer Institute (DFCI) between 2006–2011 for evaluation of a new diagnosis of AML. At the DFCI, all new patients with hematologic malignancies are asked to participate in a research protocol that involves a baseline questionnaire and prospective collection of clinical data into the Cancer Research Information System (CRIS) database. CRIS includes information collected by trained abstractors on patient demographics, initial treatment assignment, disease characteristics, pathology tests, hospitalizations, treatments and date and cause of death. We used CRIS to identify all patients ≥65 years of age who presented between January 2006 and December 2011 with a new diagnosis of AML. We excluded patients who filled out their survey after beginning chemotherapy for AML.

The survey includes items from the European Organization for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ) for the evaluation of health-related quality of life of cancer patients (QLQ-C30) (Table 2). Responses to questions about function and symptoms are rated on a scale of 1 (not at all) to 4 (very much). Chart review was performed by a trained medical student (AS) and verified by a geriatric oncologist (JD). We validated all clinical data provided by CRIS. We gathered additional information on baseline diagnosis and pathology, laboratory tests, oncologist assigned Eastern Cooperative Oncology Group (ECOG) performance status (PS) and cytogenetic data. We recorded the

course of treatment, number and length of hospitalizations, and survival. We considered inclusion of standard anthracycline and cytarabine regimens in initial treatment as induction. All patients provided written informed consent for their data to be included in the CRIS database. This study was approved by the DFCI Institutional Review Board.

Definition of predictors and outcomes

To determine if geriatric assessment variables predict mortality in our population, we selected questions from the QLQ-C30 that correspond to geriatric domains, including physical function, social function, cognition, psychological state, nutritional status, and pain (Table 2). We divided survey responses into two categories: 1–2 ("not at all" or "a little") vs. 3–4 ("quite a bit" or "very much"). We assessed comorbidities by means of the Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI), a tool designed to quantify the effect of comorbid conditions on mortality in patients with hematologic disease.[19] We defined a low albumin as < 3.5 mg/dL. We used median age at diagnosis as our age variable. We defined cytogenetic risk as favorable, intermediate, or adverse.[20] We defined overall survival (OS) as the time from the date of diagnosis of AML at DFCI to the date of death or the date of last follow-up. Disease-specific survival considered only deaths attributed to AML. Complete remission (CR) was defined according to the International Working Group.[21] There was no distinction made between those achieving CR after one or two cycles of induction chemotherapy.[22] We categorized initial treatment assignment into the following groups: induction chemotherapy, hypomethylating agents, and palliative/other therapies.

Statistical methods

We used Kaplan-Meier (KM) survival curves to describe the survival of the cohort, and to determine the univariate association between variables of interest and mortality. The log-rank test was employed to test the difference in KM curves between groups. Only variables that predicted mortality on univariate analyses ($P < 0.05$) were included in the multivariate analysis. We used multivariate Cox proportional hazard models to determine which factors were independently associated with mortality. We used Chi-squared tests to identify variables associated with reception of induction chemotherapy. We included these factors in a multivariate binary logistic regression model to determine independent predictors of receiving induction. A P-value < 0.05 was considered significant. Statistical analyses were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL).

Results

Between 2006 and 2011, 368 patients 65 and older presented to the DFCI with a diagnosis of AML. Of these, 163 (44.3%) did not complete the new patient survey prior to hospitalization for AML, 62 (16.8%) received previous chemotherapy for AML, and 42 were missing information on key variables, leaving 101 patients for the analysis. Baseline characteristics of the cohort are listed in Table 1. Overall, the cohort was white (98%), had a performance status ≤1 (79.3%), and had ≤1 comorbidity (72.4%).

About one-third (35.0%) of the patients underwent induction, 20 (19.8%) underwent consolidation chemotherapy, and 18 (17.8%) patients received stem cell therapy (SCT), most of which was non-myeloablative from a matched unrelated donor. 41.0% of patients received chemotherapy other than standard induction, and about a quarter (24%) of the cohort received only palliative or supportive care. 23% of patients received initial treatment in a clinical trial.

Self-reported geriatric assessment variables are displayed in Table 2. Answers to questions ranged from 1 (not at all) to 4 (very much) and asked patients to consider their condition in the past week. One-third of patients reported substantial ("quite a bit" or "very much") difficulty doing strenuous activities or limitations in their work or daily activities, and only 3 patients reported requiring more help with activities of daily living (ADLs) including eating, dressing, washing, and toileting. Cognitive complaints were relatively uncommon, although nearly half (47.5%) of patients reported feeling more depressed in the past week. 15.8% of patients reported substantial pain during the past week.

The median overall survival of the group was 7.8 months. The one-year OS was 37.4% and the one-year disease-specific survival was 39.0%. Survival based on demographic, tumor, treatment, and survey characteristics is presented in Table 3. As expected, median OS differed substantially by initial treatment (induction chemotherapy: 14.8 ±4.4 months versus decitabine or azacitidine: 11.4 ±1.9 months versus other therapy: 3.1 ±1.1 months versus palliative only: 3.4 ±2.4 months; $p<0.001$). A number of study variables predicted survival, in addition to the known prognostic factors. Patients reporting less difficulty with strenuous activity had increased survival compared to patients reporting more difficulty (11.8 versus 4.4 months; $P<0.001$) (Figure 1A). Less pain in the week prior to baseline was also associated with better survival (10.3 versus 4.1 months; $P<0.002$) as was HCT-CI score ≤1 versus >1 (11.8 versus 4.4 months; $P<0.001$) (Figure 1B).

On multivariate analysis (Table 4), adverse and unknown cytogenetic versus intermediate and favorable risk group (Hazard Ratio [HR], 2.61; 95%CI 1.60 to 4.25), HCT-CI score >1 versus ≤1 (HR, 1.92; 95%CI 1.18 to 3.11), more difficulty with strenuous activity versus less difficulty (HR, 2.18; 95%CI 1.19 to 4.00), and pain more versus less often (HR, 2.17; 95%CI 1.19 to 3.97) were independent prognostic factors for increased risk of death. We performed a second analysis to determine if the effect of the predictors was independent of initial treatment assignment. Both initial treatment with induction therapy (HR= 0.26; 95%CI 0.14 to 1.50) and hypomethylating agents (HR=0.39; 95%CI 0.22 to 0.68) were associated with a substantially decreased risk of mortality compared to those treated with palliative therapy. HCT-CI score (HR=1.49; 95%CI 1.36 to 3.84), difficulty with strenuous activity (HR=1.81; 95%CI 1.04 to 3.13) and pain (HR=2.55; 95%CI 1.41 to 4.64) retained significance, while cytogenetics was no longer significant (HR=2.29; 95%CI 0.90 to 2.45).

We performed a sub-analysis among the 80 patients with the best ECOG PS (0 or 1) to determine if the study variables in the final model would predict mortality in the healthiest patients. More vs. less difficulty with strenuous activities (median OS =11.8 versus 3.1 months; $P<0.001$), pain more vs. less often (median OS =10.4 versus 3.4 months; $P=0.036$), and comorbidity score >1 versus ≤1 (median OS =11.8 versus 4.8 months; $P=0.008$) remained predictors of increased risk of death.

Compared to patients who received non-intensive or supportive treatments, those who received induction were younger ($p < 0.001$), on fewer medications ($p=0.29$), had lower comorbidity scores ($p=0.002$), and less difficulty with strenuous activities ($p=0.025$). On binary logistic regression, only age at diagnosis >72 versus ≤72 (Odds ratio=23.8; 95%CI 6.30 to 90.19) and HCT-CI score >1 versus ≤1 (HR, 4.56; 95%CI 1.41 to 14.72) remained as independent predictors of not receiving IC.

Discussion

In this retrospective study of older patients with AML, we found that baseline geriatric assessment variables added valuable prognostic information to conventional clinical and pathological predictors of mortality. The model that best predicted survival in our cohort

included a disease-specific comorbidity score and self-reported measures of strenuous activity and pain in addition to cytogenetic risk group. Geriatric assessment variables remained independent predictors of mortality even among patients with the best functional status. Our study represents one of the first to use self-assessed variables to predict survival in older patients with AML, and suggests that more comprehensive risk assessment tools for this population are needed.

Although the need for geriatric assessment in oncology is well recognized, there is as yet no widely validated tool for use in oncology settings, and no instrument specific to hematologic malignancies. Well-conducted studies in general oncology populations have demonstrated that geriatric assessment in combination with conventional clinical and disease-specific factors can accurately predict vulnerability to treatment toxicity. In one prospective multicenter study, factors that independently predicted toxicity included poor hearing, falls in the past six months, difficulty managing medications, difficulty walking one block and decreased social activity, but few patients with hematologic malignancies were included. [8] A score to predict CR and early death in patients ≥ age 60 with AML who are candidates for induction has recently been developed, and is a major step forward in the effort to individualize treatment. [23] However, the tool is based on standard biological and clinical factors and does not include any measure of functional status or comorbidity. In our cohort, age itself was not an independent predictor of overall survival when other study variables were added to the model. This illustrates the need to better individualize prognosis using a multi-dimensional evaluation such as CGA.

Our findings agree with those of other studies showing that age and conventional prognostic factors do not sufficiently account for differences in survival of older AML patients [24–26], and therefore lack the necessary resolution to discriminate between good or poor candidates for intensive therapy.[3, 27] For example, while we found that self-reported physical function was associated with survival, in our cohort only a question focused on strenuous activities was predictive. This question provided more information than ECOG PS, as it was still predictive of survival even in patients with the best PS. Thus, in planning prospective geriatric assessment of candidates for induction, a more challenging functional test such as 6 minute walking speed will likely be a more helpful predictor than a standard “up and go” test. [28] On the other hand, patients who are being considered for non-intensive chemotherapy would benefit more from an assessment targeted at detecting the geriatric syndromes and frailty that would make them vulnerable to toxicity from these regimens.

Comorbidity is an important predictor of outcome in any cancer, and AML is no exception. [29] Similar to other studies, we found that a higher HCT-CI score was associated with decreased survival.[18, 30] The HCT-CI is a validated index of comorbidity found to be more sensitive than the Charlson comorbidity index for predicting non-relapse mortality and overall survival in patients with hematologic malignancies in a general AML population. [19] However, it does not contain the entire range of comorbidities found in the Charlson Index, and determining which comorbidity score is preferable in older AML patients is an important area for future work. In our study, comorbidity predicted whether patients would receive induction therapy as well as survival. It is an important and easily quantifiable factor that should be included in the risk-stratification of older patients with AML.

Pain is a highly prevalent symptom in the elderly that is intimately linked to multiple geriatric domains and health-related quality of life. Self-reported frequent pain in the week prior to AML diagnosis was a powerful prognostic indicator for worsened survival in our model. Pain has been shown to predict mortality in a general population, but the mechanisms for this relationship are unclear. [31] Bone pain from AML is not a frequent symptom at presentation in older adults, and on medical record review we found that the

majority of pain seemed to be due to non-cancer comorbidities or related to bone marrow biopsy. It is possible that pain is functioning as a marker of comorbid conditions not included in the HCT-CI score. This finding should be further explored in larger cohorts of patients with AML.

It is important to emphasize that the older patients who present to our regional cancer center are a select group with fewer comorbidities and functional limitations than expected for their age. Thus, questions in a number of geriatric domains were not predictive. Cognitive function and dependence in daily activities are usually powerful prognostic factors, but only 6.1% of our patients reported significant problems with memory and only 3% required help with activities of daily living. This also underscores the fact that geriatric oncology tools designed to detect markers of frailty in a general population may have substantial “ceiling” effects in older patients who qualify for intensive therapies or clinical trials.

As expected, initial treatment regimen was an important determinant of mortality. This reflects both the benefit of treatment, and the skill of clinicians in selecting it based on patient factors such as comorbidity and functional status. We found that comorbidity score and self-reported measures of physical function and pain were predictors of outcome independent of treatment assignment, suggesting that they are useful across a wide range of patient characteristics. Previous studies in older adults with AML have shown that patients with better PS and fewer comorbidities have increased survival after induction.[32] A study of AML patients ≥ age 70 suggested that induction may only be beneficial for survival in a small subset of patients based on age, PS, tumor karyotype, and creatinine level, but [33] this study did not include geriatric assessment. In our cohort, age and comorbidity were the only independent prognostic factors for reception of induction chemotherapy, but as only 35 patients received induction, the power for this analysis was limited. Ongoing studies incorporating geriatric assessment in the care of older patients with AML will help develop tools to improve selection of older patients for aggressive treatment. [9]

Our work has a number of limitations. As a single-institution study, the population seen at DFCI for treatment of AML is highly select. The patients that agreed to complete our surveys were likely the least sick, and they were seen in the outpatient setting prior to hospitalization. Furthermore, patients with AML admitted first as inpatients were excluded from the study as they completed the new patient survey after initiating chemotherapy. While these factors limit generalizability, the fact that geriatric assessment variables predict outcome even in this population suggest their value in a more general one, as this selection bias would influence our results toward the null. In this exploratory analysis, we used self-reported variables from a validated quality of life survey that was not designed for geriatric patients. True geriatric assessment involves the use of validated instruments for evaluation of specific domains such as mood and cognition, for which objective analysis is critical. Nevertheless, we found that self-reported variables on physical function and pain were helpful predictors of outcome, suggesting that true geriatric assessment would provide even more valuable information. Finally, we did not have information on molecular genetics, a new and important prognostic indicator in AML.

In conclusion, our study provides evidence that assessment of geriatric domains adds important prognostic information over and above that of established laboratory and clinical factors in older patients with AML, even among those with an excellent performance status and relatively few comorbidities. Our data suggest that in a highly select population such as patients being considered for induction therapy, assessments must be targeted at higher levels of function. Further studies in larger cohorts of elderly patients with AML are needed to better define the geriatric domains that are most valuable in predicting prognosis in combination with known prognostic factors and new molecular genetic techniques.

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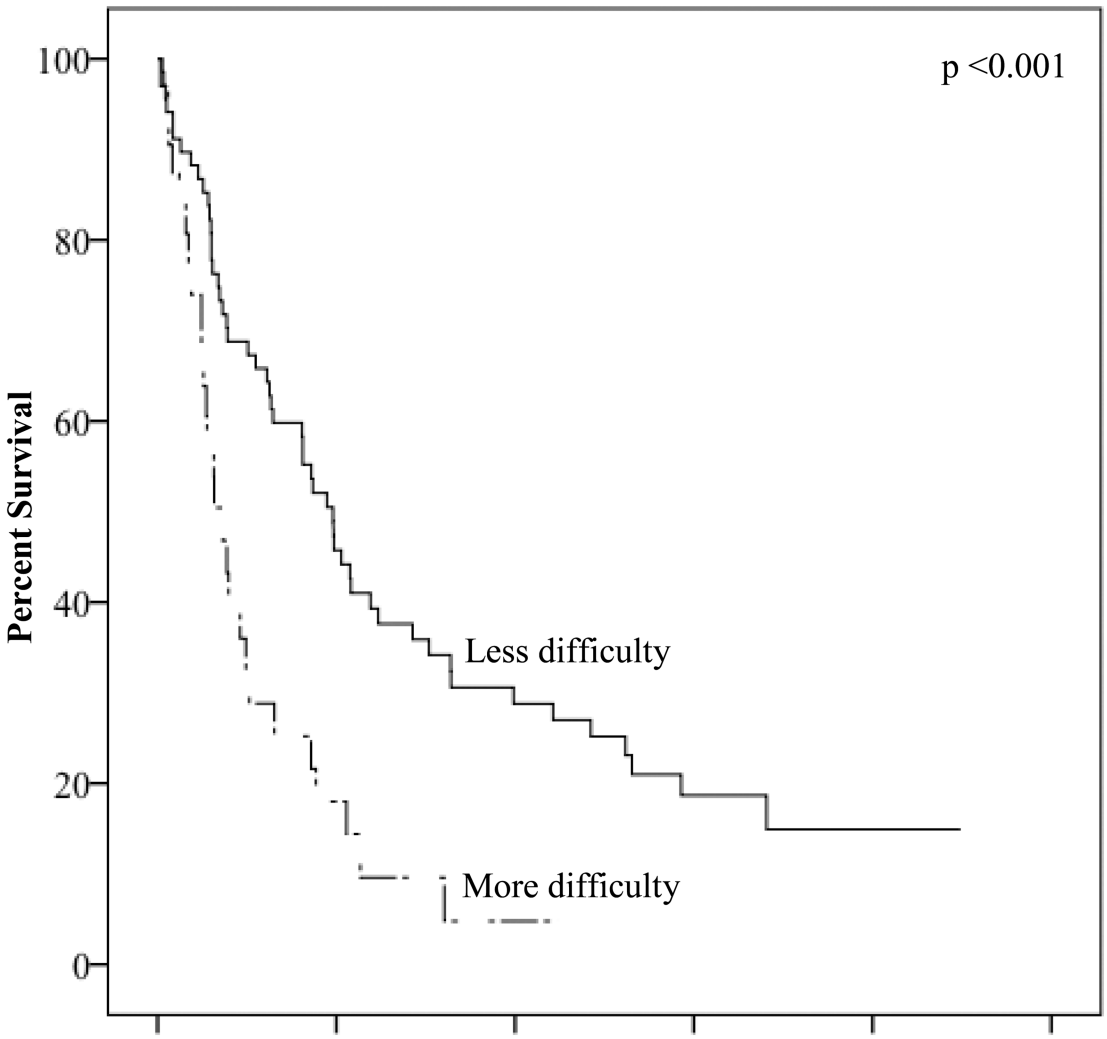
A.



Numbers at risk						
Less Difficulty	68	29	16	8	2	0
More Difficulty	33	5	1	0	0	0

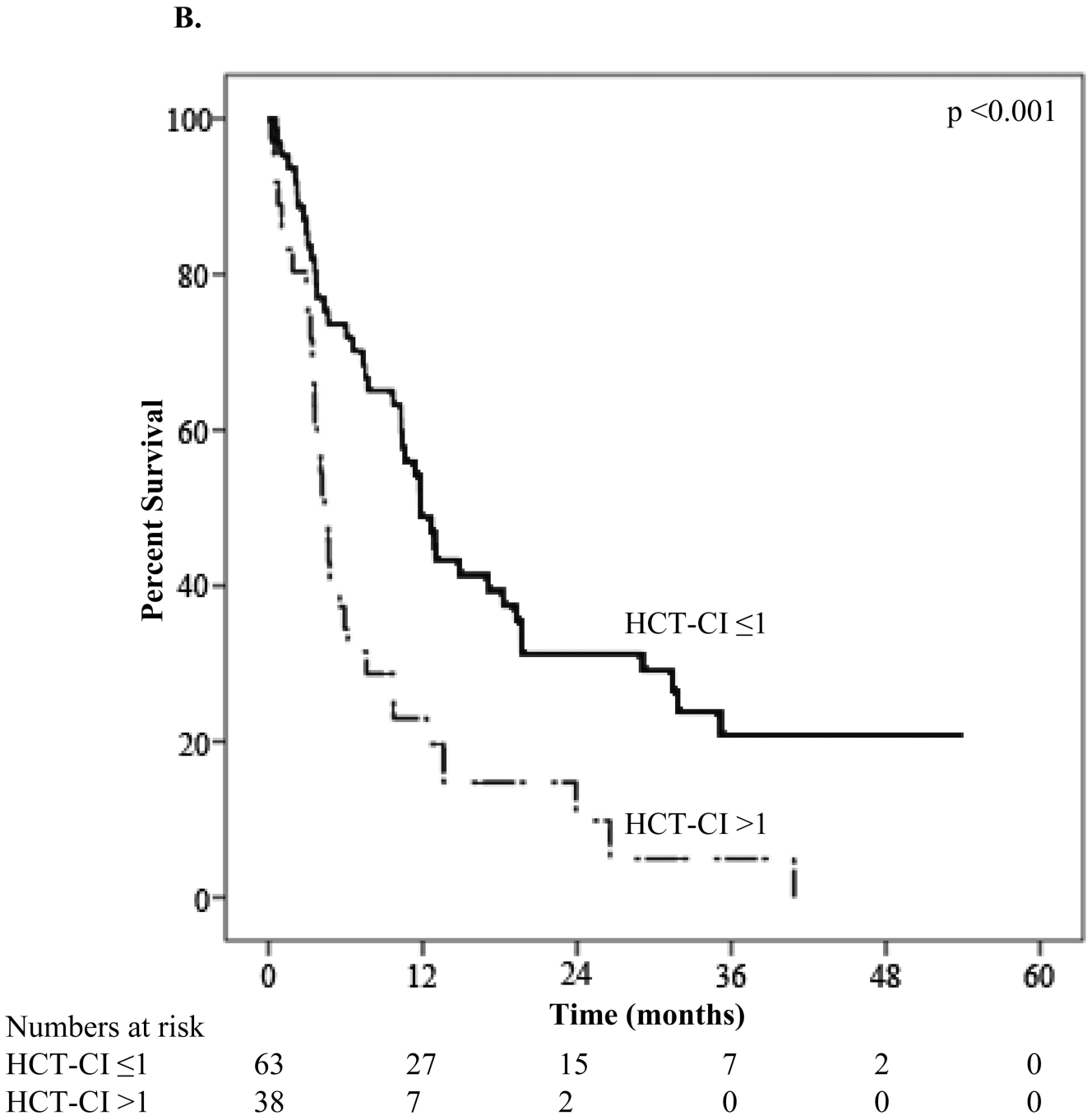


Figure 1.

A. Kaplan-Meier survival curve stratified by difficulty with strenuous activity

B. Kaplan-Meier survival curve stratified by HCT-comorbidity index

Table 1

Demographic and clinico-pathologic characteristics

Characteristic	N (%)
Age at diagnosis (years)	
65–70	41 (40.6%)
71–75	24 (23.8%)
75–80	20 (19.8%)
>80	16 (15.8%)
Male	63 (62.4%)
White	99 (98.0%)
BMI (kg/m^2), mean ±SD	27.9 ±4.9
Physician-rated ECOG PS	
0	25 (24.8%)
1	55 (54.5%)
2	17 (16.8%)
3	4 (4.0%)
HCT-comorbidity index	
≤1	64 (63.4%)
>1	37 (36.6%)
Number of medications, mean ±SD	5 ±3
History of tobacco use	59 (59.6%)
Family history of hematologic malignancy	15 (14.9%)
Origin of disease	
De novo	55 (54.5%)
Secondary to MDS	34 (33.7%)
Treatment-related	12 (11.9%)
Cytogenetic risk group	
Favorable	2 (2.0%)
Intermediate	47 (46.5%)
Adverse	32 (31.7%)
Unknown	20 (19.8%)
Percent blasts in bone marrow, mean ±SD	40.7 ±24.2
Initial treatment Received	
Induction chemotherapy	35 (35.0%)
Decitabine or Azacitidine	34 (34.0%)
Other *	7 (7.0%)
Palliative only	24 (24.0%)
Consolidation chemotherapy	20 (19.8%)
Stem cell therapy	18 (17.8%)
Initial treatment on clinical trial	23 (23.0%)
Patients achieving complete response by initial treatment	
Induction chemotherapy	25 (71.4%)

Characteristic	N (%)
Decitabine or Azacitidine	2 (5.9%)
Other *	0 (0.0%)
Palliative only	0 (0.0%)
Relapse	12 (11.9%)

* Other includes oral 6-mercaptopurine, Iressa clinical trial (CT), FLT3 inhibitor with mTOR inhibitor CT, CT with Revlimid and Velcade, histone deacetylase inhibitor CT, Cloretazine CT, and all-trans retinoic acid

Abbreviations: BMI, body mass index; ECOG PS, *Eastern Cooperative Oncology Group Performance Status; HCT, Hematopoietic Cell Transplant; MDS, myelodysplastic syndrome*

Table 2

EORTC QLQ-C30 questions by geriatric domain

Domain	Question†	N (%) patients responding‡	
		Less	More
Physical Functioning	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	64 (66.0%)	33 (34.0%)
	Do you need help with eating, dressing, washing yourself or using the toilet?	95 (96.9%)	3 (3.1%)
	Were you limited in doing either your work or other daily activities?	67 (67.0%)	33 (33.0%)
Social Functioning	Were you limited in pursuing your hobbies or other leisure time activities?	67 (70.5%)	28 (29.5%)
	Has your physical condition or medical treatment interfered with your family life?	87 (87.0%)	13 (13.0%)
	Has your physical condition or medical treatment interfered with your social activities?	77 (77.0%)	23 (23.0%)
Cognitive Functioning	Have you had difficulty remember things?	92 (93.9%)	6 (6.1%)
	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	94 (93.1%)	7 (6.9%)
Psychological State	Did you worry?	77 (78.6%)	21 (21.4%)
	Did you feel depressed?	52 (52.5%)	47 (47.5%)
Nutritional Status	Have you lacked appetite?	79 (79.0%)	21 (21.0%)
Pain Status	Have you had pain?	85 (84.2%)	16 (15.8%)

† Questions ask patient to consider the past week

‡ More indicates “Quite a Bit” or “Very Much”; Less indicates “Not at All” or “A Little”

Table 3

Kaplan-Meier survival estimates based on patient and tumor characteristics

Characteristic	Median OS* (months)	1-year OS (% survival)	2-year OS (% survival)	P-value*
Age at diagnosis (years)				<0.001
≤72	12.3 ±1.9	51.4 ±7.2	32.8 ±7.0	
>72	4.7 ±1.2	22.2 ±6.2	10.3 ±4.7	
BMI (kg/m^2)				0.095
<28	4.8 ±1.1	31.6 ±6.6	20.4 ±5.9	
≥28	11.8 ±1.1	47.2 ±7.8	24.9 ±7.1	
Albumin				0.062
Normal	9.7 ±1.9	40.3 ±5.4	23.6 ±4.9	
Low (<3.5g/dL)	3.0 ±1.2	18.8 ±11.9	9.4 ±8.9	
HCT-comorbidity index				<0.001
≤1	11.8 ±1.2	48.8 ±6.6	31.3 ±6.3	
>1	4.4 ±0.5	23.0 ±7.1	9.8 ±6.0	
ECOG PS				0.015
≤1	10.3 ±1.0	40.8 ±5.8	28.8 ±5.6	
>1	4.4 ±0.7	33.3±10.3	5.6 ±5.4	
Origin of AML				0.022
De novo	11.8 ±2.0	46.9 ±7.0	31.1 ±6.8	
Secondary	6.6 ±1.3	29.3 ±7.1	14.2 ±5.9	
Cytogenetic risk group				0.001
Favorable	**	**	**	
Intermediate	12.9 ±1.7	53.5 ±7.6	37.2 ±7.7	
Adverse	6.6 ±2.0	26.9 ±8.0	3.4 ±3.3	
Peripheral blast percent				0.022
≤8%	11.4 ±1.0	44.5 ±7.2	34.1 ±7.2	
>8%	6.1 ±2.0	32.6 ±7.1	12.9 ±5.2	
Initial Treatment				<0.001
Induction chemotherapy	14.8 ±4.4	60.1 ±8.6	39.1 ±8.9	
Decitabine or Azacitidine	11.4 ±1.9	45.0 ±9.0	18.2 ±7.6	
Other	3.1 ±1.1	14.3 ±13.2	**	
Palliative only	3.4 ±2.4	4.2 ±4.1	**	
Complete response achieved				<0.001
No	4.7 ±1.0	24.4 ±5.4	14.4 ±4.5	
Yes	23.9 ±6.7	76.8 ±8.3	48.0 ±10.7	
Stem cell therapy (SCT)				<0.001
No SCT	5.9 ±1.4	25.9 ±5.1	15.6 ±4.3	
Yes SCT	29.1 ±9.1	88.9 ±7.4	50.8 ±12.5	
Strenuous activity difficulty				<0.001
Less difficulty	11.8 ±1.4	45.8 ±6.1	28.8 ±5.8	
More difficulty	4.4 ±0.9	18.0 ±7.2	4.8 ±4.5	

Characteristic	Median OS* (months)	1-year OS (% survival)	2-year OS (% survival)	P-value*
Pain in last week				0.022
Less often	10.3 ±2.0	42.5 ±5.6	27.6 ±5.3	
More often	4.1 ±1.0	20.0 ±11.3	**	

* OS=Overall survival

* P-values calculated using log-rank test

** Too few patients to calculate

Table 4

Multivariate analysis of prognostic factors for increased risk of death

Factor	Hazard Ratio	95% CI*
Cytogenetics[α]	2.61	1.60–4.25
HCT-CI score[β]	1.92	1.18–3.11
Difficulty with strenuous activity[γ]	2.18	1.19–4.00
Pain[δ]	2.17	1.19–3.97
ECOG PS[ε]	0.96	0.50–1.83
Origin of AML[δ]	1.18	0.74–1.89

*Hazard Ratios and 95% confidence intervals estimated by Cox proportional hazards models.

[α]Adverse and unknown vs. Intermediate and favorable

[β]HCT-CI score >1 vs. ≤1

[γ]More difficulty vs. less difficulty

[δ]Pain more often vs. less often

[ε]ECOG PS >1 vs. ≤1

[ζ]Secondary vs. de novo