Quality of life in elderly patients with acute myeloid leukemia: patients may be more accurate than physicians

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ABSTRACT

Background
The aim of this study was to evaluate changes in quality of life scores and their association with therapy and survival in unselected elderly patients with acute myeloid leukemia.

Design and Methods
From February 2003 to February 2007, 113 patients aged more than 60 years with *de novo* acute myeloid leukemia were enrolled in a prospective observational study. Two different quality of life instruments were employed: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30 (EORTC QLQ-C30) and a health-related quality of life questionnaire for patients with hematologic diseases (QOL-E).

Results
Forty-eight patients (42.4%) received intensive chemotherapy and 65 (57.6%) were given palliative treatments. Age greater than 70 years (P=0.007) and concomitant diseases (P=0.019) had a significant impact on treatment allocation. At diagnosis, general quality of life was affected [median QOL-E standardized score 54, interquartile range 46-70; median EORTC global score 50, interquartile range 41-66]. Most patients were given a good ECOG Performance Status (< 2), which did not correlate with the patients' perception of quality of life. At multivariate analysis, palliative approaches (P=0.016), age more than 70 years (P=0.013) and concomitant diseases (P=0.035) each had an independent negative impact on survival. In a multivariate model corrected for age, concomitant diseases and treatment option, survival was independently predicted by QOL-E functional (P=0.002) and EORTC QLQ-C30 physical function (P=0.030) scores.

Conclusions
Quality of life could have an important role in elderly acute myeloid leukemia patients at diagnosis as a prognostic factor for survival and a potential factor for treatment decisions.

Key words: AML, elderly, intensive chemotherapy, quality of life.

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Introduction

Acute myeloid leukemia (AML) is a hematologic disease which occurs prevalently in elderly subjects, with the median age of incidence being over 65 years.[1] The treatment of elderly patients with AML is still a matter of debate, as intensive chemotherapy leads to unsatisfactory results in this subset, with dismal complete remission, disease-free survival and overall survival rates compared with those in younger patients.[2-5] Age-related factors,[6,7] poor Performance Status and a higher incidence of poor-risk cytogenetics, multi-drug resistance and treatment-related mortality[8] contribute to these scarce results. In addition, many elderly AML patients are unfit for intensive chemotherapy and are generally managed with palliative approaches.[9]

Quality of Life (QoL) is one of the most important patient-reported outcomes. Measurement of QoL at diagnosis may provide useful information regarding patients' preferences and prognosis, while follow-up measurements may indicate acceptance, adaptation and adverse effects of disease and therapy.[10-12] QoL has been widely explored in many diseases and its change is a primary endpoint of many clinical trials.

Several instruments to evaluate QoL have been validated over the past years and are now available.[13] Among specific modular disease-oriented questionnaires, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire – C30 (EORTC QLQ-C30) has been used worldwide to evaluate QoL in cancer patients.[14,15] Recently, a health-related quality of life questionnaire for patients with hematologic diseases (QOL-E) has been reported and validated in patients affected by myelodysplastic syndromes;[16-18] its role in elderly patients with AML, which is closely related to myelodysplastic syndromes, is investigated in this study.

In the past years, the prognostic significance of QoL scores measured at disease onset have been reported in some oncologic diseases;[19,20] however, their role is less known in the hematologic setting,[21] in particular, in elderly patients with AML.

The objectives of this prospective, national, multicenter, 12-month observational study were to evaluate QoL scores at diagnosis and their association with disease factors, therapy and survival in a cohort of consecutive, unselected elderly patients with *de novo* AML.

Design and Methods

Patients

All patients aged over 60 years with newly diagnosed *de novo* AML according to the World Health Organization classification[20] were consecutively enrolled in the trial in four hematology centers, irrespectively of the patients' clinical conditions at onset and the therapeutic approach. All patients gave written informed consent to participation in the study, in accordance with institutional regulations. The study was approved by the local Ethical Committees and the procedures followed were in accordance with the Helsinki Declaration (1964, and its subsequent amendments) of the World Medical Association.

Patients with secondary AML, acute promyelocytic leukemia or concomitant solid cancers, as well as patients unable to respond to the QoL questionnaires because of neurological or psychiatric disorders, were considered ineligible for the study.

Data on hematologic variables and concomitant diseases were collected throughout the study. Any clinical illness was considered as a concomitant disease if requiring a specific and prolonged treatment: for example, mild arterial hypertension or diabetes requiring only dietary management were not considered concomitant diseases.

Chemotherapy

AML therapy was not restricted by protocol and was given freely at each of the centers according to individual clinicians' choice. The various treatment schemes were divided into two broad groups: intensive therapies and palliative treatments. Intensive therapies included all therapies aimed mainly at achieving a complete remission with possible cure of the disease and generally consisted of the standard anthracycline plus cytarabine association or intermediate/high-dose cytarabine, with or without additional drugs. Palliative treatments ranged from supportive care only, aimed mainly at controlling disease symptoms and complications, to low-dose chemotherapy to contain disease burden and, possibly, prolong survival.

Quality of life assessments

The QOL-E v.2 and the EORTC QLQ-C30 questionnaires *(Online Supplementary Materials)* were self-administered by patients or completed with the aid of an independent individual, not related to the patient and blind to the clinical results. The questionnaires were completed at diagnosis by all patients.

QOL-E version 2

QOL-E v. 2 is a myelodysplastic syndrome-specific QoL instrument consisting of a 28-item questionnaire. It comprises two items concerning general perception of well-being, four items addressing physical well-being (QOL-FIS), three items on functional well-being (QOL-FUN), four items on social well-being (QOL-SOC), two items on sexual well-being (QOL-SEX), seven items related to fatigue (QOL-FAT) and seven disease-specific items (QOL-MDSS). Each item has Likert-scale response options. A treatment-outcome-index domain (QOL-TOI) is derived from the sum of QOL-FIS, QOL-FUN and QOL-MDSS. The QOL-E instrument has adopted the HNQoL instrument scoring system. Each item is re-scaled so that better health corresponds with a higher numerical value. After the items are re-scaled, raw scores can be generated for each scale by adding together the responses for all items in that scale. No question is weighted more heavily than another: the re-scaled item scores are simply added to generate a raw score. Transformation of raw scores into a scale from 0 to 100 is performed to generate the standardized score according to the following formula:

standardized score = [(actual raw score - lowest possible raw score)/possible raw score range] x 100.

The standardized scale has a possible range of scores from 0 to 100. Higher scores indicate better health for each domain.

EORTC QLQ-C30 version 3

The EORTC QLQ-C30 v. 3 questionnaire consists of five functional scales (physical, role, emotional, cognitive, social), symptom scales, and one global scale. All measures are scaled from 0 to 100 with the same direction as QoL-E, but higher scores in symptom scales indicate a more severe problem (i.e. more severe symptoms).

Statistical methods

Normally distributed data are expressed as the mean ± standard deviation, while non-normally distributed data are expressed as the median and interquartile range (IR) if continuous, and as per-

centage frequencies if categorical; bootstrap samples of the sample medians were generated to construct confidence intervals (CI) for the medians. Within-patient comparisons were made by the paired t-test and χ^2 test, as appropriate; *P* values less than 0.05 are considered statistically significant. The relationship between paired variables was analyzed by Pearson's product moment correlation coefficient. Cronbach's alpha standardized coefficients were calculated for the evaluation of the reliability and internal consistency of the QoL questionnaires: an alpha coefficient of 0.70 or higher was considered sufficient for the purpose of group comparisons.

Univariate and multivariate regression models were used to associate and/or predict the effects of treatment with response, duration of response and the composite scores of QOL-E and EORTC QLQ-C30 at baseline.

For survival analysis, univariate Kaplan-Meier and multivariate Cox analysis were performed.

All calculations were made using a standard statistical package (SPSS for Windows Version 15.0; Chicago, IL, USA).

Results

Patients and treatments

From February 2003 to February 2007, 113 elderly AML patients (males 58, females 55; mean age 71.7±5.9 years) were consecutively enrolled in the study. Their clinical characteristics at onset of AML are shown in Table 1.

According to the Eastern Cooperative Oncology Group (ECOG) scale, Performance Status at disease onset was reported by the physician to be 0 or 1 in 101 patients (89.4%) and 2 or more in the remaining 12 patients (10.6%). At least one concomitant severe disease requiring treatment was present in 68/113 patients (60.1%): in addition, 17 patients (15%) had more than one concomitant disease at onset. The most frequently reported concomitant diseases were arterial hypertension (29 patients), ischemic cardiovascular diseases (20 patients), diabetes (18 patients), chronic respiratory diseases (9 patients) and chronic gastrointestinal diseases (6 patients).

According to physicians' decision, 48 patients (42.4%) received intensive therapy while 65 (57.6%) were assigned to palliative treatment, which consisted of supportive care only in 38 cases. The clinical features of patients divided according to treatment allocation are reported in Table 1. The different intensive and palliative schemes are summarized in Table 2.

Age and concomitant diseases had a significant impact on therapeutic decisions. In particular, 68% of patients in the palliative treatment group *versus* 40% in the intensive treatment group were over 70 years old (*P*=0.007). At least one concomitant disease was present in 70% of patients in the palliative treatment group and 48% of those in the intensive treatment group (*P*=0.019). Among patients with concomitant diseases, a palliative approach was chosen for 77% of patients over 70 years old and for 48% of those under 70 years old (*P*=0.032). In contrast, in patients without concomitant diseases at diagnosis, age did not influence the treatment decision (*P*=0.361). Symptoms and peripheral blood or bone marrow features at diagnosis were not predictive of treatment allocation.

Quality of life scores

Median QoL scores at diagnosis are shown in Table 3. Both questionnaires showed that general QoL was affected: the median QOL-E general standardized score and the median EORTC global score were 54 (IR 46-70) and 50 (IR 41-66), respectively. Loss of appetite was perceived by 75% of patients and fatigue scores were low, indicating poorer QoL, in both questionnaires (QOL-E median score 45, IR 32-53; EORTC-QLQ C30 median score 33, IR 22-66).

There was no significant correlation between treatment allocation and any score in either questionnaire (Table 3).

At univariate analysis, there was a significant correlation between fatigue and age, hemoglobin levels and the duration of fever. In a multivariate regression model, both hemoglobin and age independently predicted fatigue (linear R^2 0.114, *P*=0.001; and linear R^2 0.066, *P*=0.01, respectively).

Patient-assessed quality of life versus *physician-assessed Performance Status*

As reported above, the vast majority of patients were considered to have a good ECOG Performance Status (< 2) by physicians (hematologists) at diagnosis. Interestingly, the scale did not identify the patients' (subjective) perception of QoL, in particular concerning physical and fatigue scores (Figure 1), as many patients who perceived that they had a poor health status (QoL score < 60) were considered in good health (ECOG Performance Status 0-1) by physicians.

Table 1. Patients' clinical characteristics at onset and differences between treatment groups at univariate analysis.

	Overall population	IT group	PT group	*P*
Age, mean±SD	71.7±5.9	69±5	74±6	<0.0001
Hemoglobin g/dL, mean±SD	8.9±1.6	10.5±0.8	9.1±1.8	0.101
Platelets×10⁹/L median (IR)	52 (25-93)	58 (24-92)	50 (28-99)	0.796
WBC×10⁹/L, median (IR)	3.8 (1.7-20.8)	3.1 (1.3-10.1)	4.0 (1.9-26.8)	0.054
Peripheral blasts %, median (IR)	32 (7-72)	30 (5-74)	31 (8-70)	0.638
Marrow blasts %, median (IR)	68 (41-85)	69 (46-89)	68 (37-83)	0.369
Fever (yes/no)	19/94	10/38	9/56	0.303
Hemorrhages (yes/no)	9/104	5/43	4/61	0.497
Concomitant diseases (yes/no)	68/45	23/25	45/20	0.019
ECOG Performance Status scores 0/1/2/3/4	52/49/10/1/1	26/21/2/0/0	30/24/8/1/1	0.254

IT: intensive therapy; PT: palliative treatment; WBC: white blood cells; SD: standard deviation; IR: interquartile range.

Table 2. Frequencies of induction treatments.

	Cases treated (%)
Intensive therapies	
Anthracycline + cytosine arabinoside + 3rd drug	16
Anthracycline + cytosine arabinoside	32
Palliative treatments	
Cytosine arabinoside +/- 2nd drug	11
Hydroxyurea	8
Mylotarg (anti CD33)	8
Supportive care only	38

Survival and prognostic factors

At the end of the observation period of 12 months, 46 patients had died; the median overall survival was 49 weeks (95% CI: 34-63 weeks).

At univariate Kaplan-Meier survival analysis, overall survival was longer in younger patients (≤ 70 years) with a median not reached after 1 year compared to older patients who had a median survival of 16 weeks (95% CI: 4–27 weeks; *P*<0.0001) (Figure 2A). Patients with concomitant diseases had a median survival of 33 weeks (95% CI: 15–52 weeks), which was significantly shorter than that of patients without concomitant diseases (median not reached; *P*=0.014). Patients receiving intensive treatment had a longer survival than patients receiving palliative care (median not reached and 72% of patients surviving at 1 year *versus* 20 weeks, 95% CI: 8-33 weeks, respectively; *P*<0.0001) (Figure 2B); however, in the subgroup of patients over 70 years old, intensive treatment was associated with a significantly shorter survival (*P*=0.003). ECOG Performance Status scores did not distinguish patients according to survival.

At multivariate Cox survival analysis, controlling for age category, presence/absence of concomitant diseases and treatment group and correcting for the center-effect, independent predictors of survival were age, concomitant diseases and treatment allocation. In detail, mortality risk was 2.4 times higher for patients over 70 years old compared to younger patients (95% CI: 1.2–5.1; *P*=0.013); 2.0 times higher for patients with concomitant diseases (95% CI: 1.1–4.0; *P*=0.035); and 2.7 times higher for patients receiving palliative treatment (95% CI: 1.2–5.9; *P*=0.016).

Survival and quality of life

Quality of life scores at diagnosis discriminated patients according to overall survival. Patients with low scores (<60) had shorter survival compared to those with higher scores: QOL-E functional score (median 15 weeks, 95% CI 12–17 weeks *versus* 55 weeks, 95% CI 42-69 weeks; *P*=0.002), QOL-E physical score (median 18 weeks, 95% CI 0–37 weeks *versus* 60 weeks, 95% CI 34-87 weeks; *P*=0.038), EORTC-QLQ C30 physical function (median 14 weeks, 95% CI 5-24 weeks *versus* 60 weeks, 95% CI 44-77 weeks; *P*<0.0001), EORTC-QLQ C30 role function (median 21 weeks, 95% CI 7-36 weeks *versus* 55 weeks, 95% CI 32–79 weeks; *P*=0.015) and EORTC-QLQ C30 fatigue score (median 14 weeks, 95% CI 13-15 weeks *versus* 55 weeks, 95% CI 46-65 weeks; *P*=0.004).

In order to evaluate the predictive value of QoL at diagnosis for survival, a multivariate Cox model was constructed controlling for age, concomitant diseases and

Table 3. Median QoL scores and 95% bootstrap confidence intervals (95% CI) of medians of the whole sample and according to treatment allocation.

	Whole group Median (95%CI)*	IT group Median (95%CI)*	PT group Median (95%CI)*	*P*
QOL-E				
Physical	70 (60-70)	70 (60-70)	70 (60-75)	0.733
Functional	69 (62-69)	69 (54-84)	69 (54-69)	0.464
Social	67 (56-67)	67 (56-78)	61 (50-67)	0.216
Fatigue	45 (36-49)	40 (36-47)	49 (36-53)	0.533
Disease-specific	35 (30-35)	35 (30-41)	35 (24-41)	0.535
General	54 (51-62)	57 (51-64)	54 (37-72)	0.502
EORTC QLQ-C30				
Global Health Status	50 (50-58)	50 (50-67)	50 (50-58)	0.660
Physical	67 (60-73)	67 (60-73)	67 (60-80)	0.656
Role function	67 (67-67)	67 (67-83)	67 (67-67)	0.083
Cognitive	83 (83-100)	100 (83-100)	83 (83-100)	0.524
Social	83 (83-100)	83 (83-100)	83 (83-100)	0.437
Fatigue	33 (33-44)	33 (33-44)	33 (33-53)	0.235
Vomiting	0 (0-0)	0 (0-17)	0 (0-0)	0.113
Pain	0 (0-17)	0 (0-17)	0 (0-17)	0.968
Insomnia	0 (0-33)	0 (0-33)	0 (0-33)	0.646
Appetite loss	33 (0-33)	33 (0-33)	33 (0-33)	0.855
Constipation	0 (0-33)	0 (0-0)	33 (0-33)	0.052

**95% Bootstrap confidence interval of medians of sample median; IT: intensive therapy; PT: palliative treatment.*

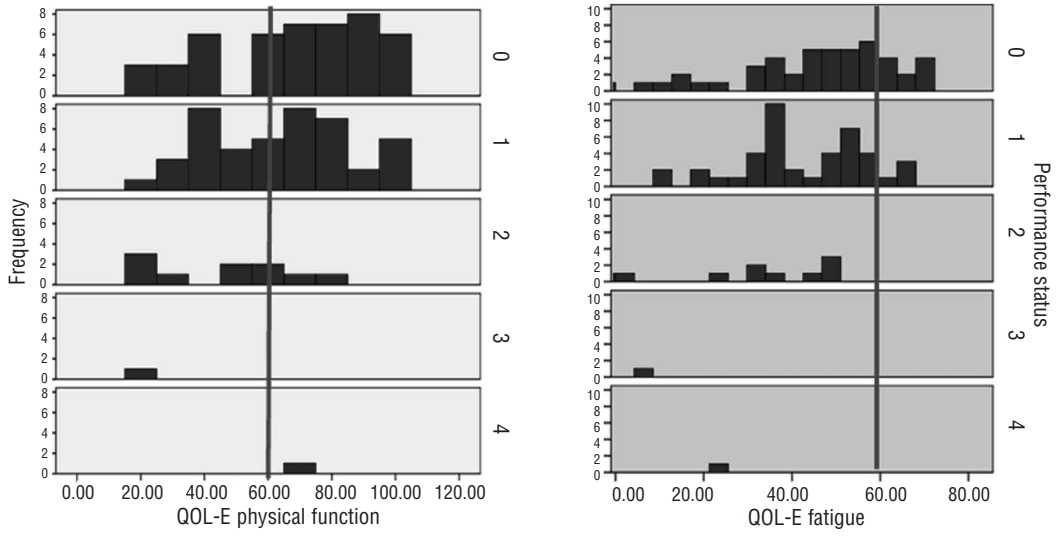

Figure 1. Comparison between medical evaluation of ECOG Performance Status and patients' subjective QoL evaluation at diagnosis.

treatment option: in this model, QoL measures that independently predicted survival were QOL-E functional scores (P=0.002; Figure 3A) and EORTC QLQ-C30 physical function scores (P= 0.030; Figure 3B).

Among patients with an ECOG Performance Status score of 0, 27% had EORTC QLQ C30 physical function scores less than 60 (poor QoL) and had a significantly shorter survival (Figure 4A). A similar proportion (33%) perceived poor QOL-E functional scores and also experienced a shorter survival (Figure 4B).

The predictive value of QoL on survival was mainly observed in older patients (over 70 years of age) receiving palliative treatment: those with poor functional QOL-E at diagnosis had a significantly shorter survival than those with good QoL (median 14 weeks, 95% CI 6-22 weeks *versus* median 27 weeks, 95% CI 2-51 weeks; P<0.0001). This finding was confirmed by the physical function EORTC QLQ-C30 scores (P=0.004) (Figure 3C). Furthermore, in those particularly elderly patients with good QoL scores at diagnosis, palliative care was associated with a significant survival advantage.

The well-known effect of age on survival was confirmed among patients receiving palliative therapy with poor functional QOL-E scores; the median survival was not reached in younger patients (< 70 years) while in older patients it was 14 weeks (95% CI: 6-22 weeks; P<0.0001).

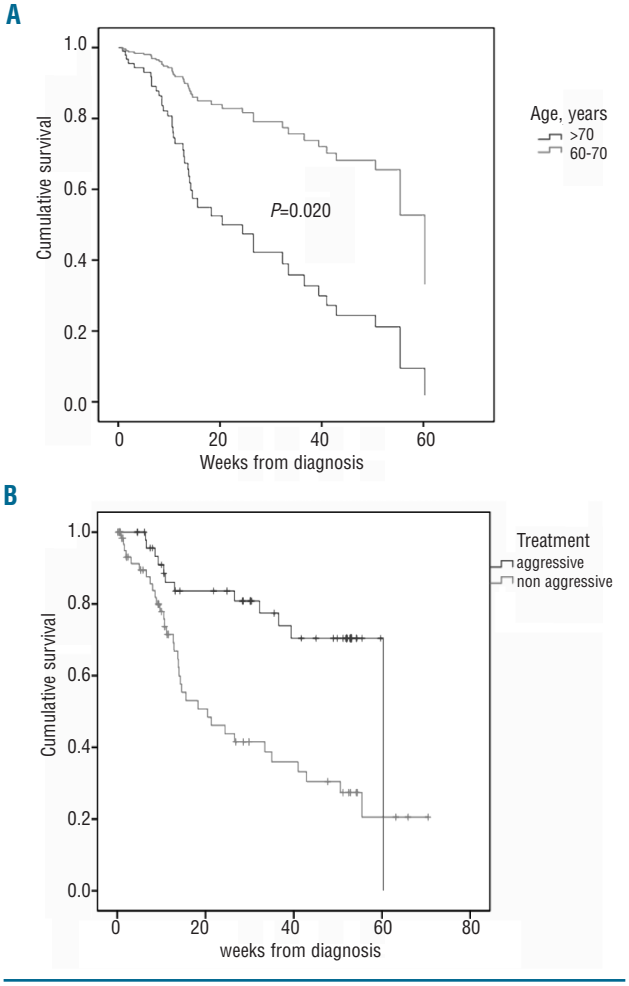

Figure 2. Survival according to (A) age and (B) treatment allocation.

The survival of younger patients receiving intensive treatment was independent of baseline QOL-E functional measures (median not reached; P=0.617).

Discussion

The evaluation of QoL is currently a major factor in decision-making for patients with solid and hematologic tumors. There are, however, several issues regarding the validity of results obtained by QoL measures, such as the

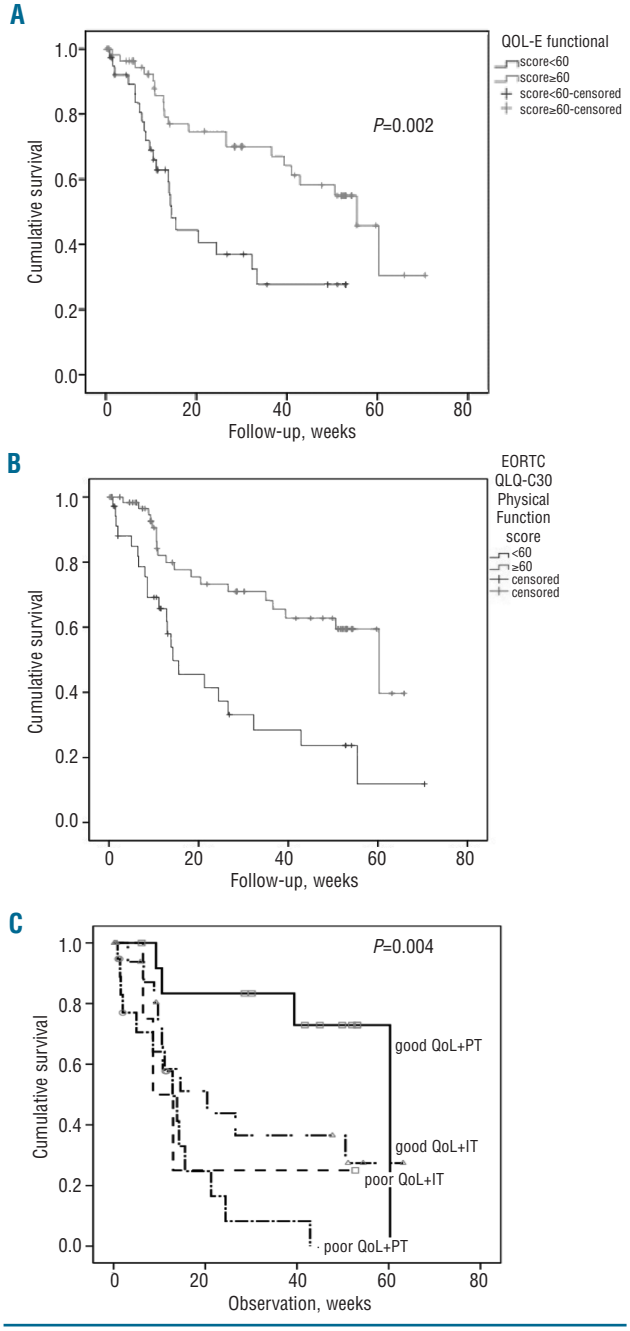

Figure 3. Survival according to QoL scores: (A) QOL-E functional and (B) EORTC QLQ-C30 physical function. (C) Survival according to EORTC-QLQ C30 physical function scores and treatment allocation in patients over 70 years of age.

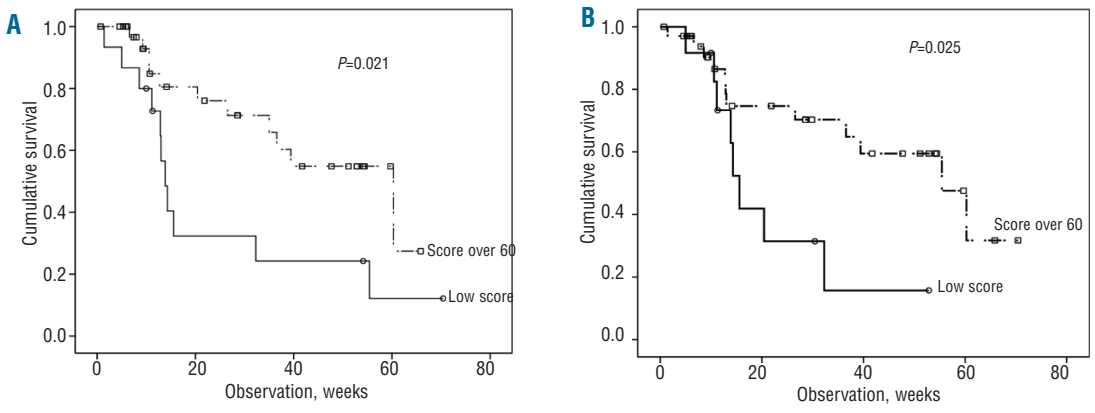

Figure 4. In patients assigned an ECOG Performance Status score of 0, differences in survival according to (A) EORTC QLQ-C30 physical function scores and (B) QOL-E functional scores.

large number of QoL scales and their inter-correlations.[23] The selection of a particular set of scores becomes difficult since many scores may predict survival equally when analyzed with clinical factors. Furthermore, 'outliers' may neutralize final results (i.e. patients with very poor scores may have a prolonged survival and *vice versa*).

Nonetheless, it is becoming clear that QoL might have a prognostic impact in oncology. In fact, recent studies in patients with solid tumors showed that QoL and cognitive functioning were statistically significant prognostic factors for survival.[24-26] However, there are no previously published data on QoL in elderly patients with AML.

Some of the findings of our study deserve comment: first, both the QOL-E and the EORTC QLQ-C30 questionnaires have been shown to be informative instruments for evaluating QoL in AML. At diagnosis, general QoL was compromised. Both questionnaires revealed that fatigue was a prevalent condition compromising QoL in this setting. QoL was associated with age and hemoglobin values. Based on clnical practice, these findings were not surprising.

In contrast, an unexpected finding of this study was the lack of correlation at diagnosis between medical assessment of physical function by ECOG Performance Status scores and patient-reported outcomes (QoL). Since the type of therapy (aggressive *versus* palliative *versus* experimental) is frequently conditioned by medical judgment and eligibility criteria based on ECOG Performance Status score, it is noteworthy that patients might be erroneously allocated to a given treatment group without a QoL evaluation. The results indicate that patients with poor functional QoL scores but in a favourable ECOG Performance Status group have a shorter survival compared to patients with good functional QoL assigned to the same treatment group. Whether patients require different therapeutic approaches according to self-assessed QoL remains to be investigated.

As regards prognostication, the already reported predictive value of age, treatment allocation and concomitant diseases for survival was confirmed in this study.[27] QoL at diagnosis was shown to be an innovative and additional independent predictor. Its evaluation is particularly useful in patients over 70 years of age in whom perception of functional well-being, as assessed by both questionnaires, seemed to be a powerful predictor of survival. According to the results of the present study, the appropriate management for particularly elderly patients with good QoL may be palliative care, since such patients may benefit in terms of survival.

In conclusion, although QoL is highly subjective, we outline the role of its values in elderly AML patients at diagnosis as a prognostic factor for overall survival and, thus, as a potential variable that may be integrated in the process of decision-making for treatment allocation.

Authorship and Disclosures

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