Do quality of life or physical function at diagnosis predict short-term outcomes during intensive chemotherapy in AML?

N. Timilshina1, H. Breunis1, J. M. Brandwein2, M. D. Minden3, V. Gupta3, S. O’Neill4, G. A. Tomlinson5,6, R. Buckstein8, M. Li7 & S. M. H. Alibhai1,4,8*

1Department of Medicine, University Health Network, Toronto; 2Division of Hematology, Department of Medicine, University of Alberta, Edmonton; 3Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto; 4Institute of Health Policy, Management, and Evaluation; 5Department of Public Health Sciences; 6Hematology/Oncology, Sunnybrook Odette Cancer Center; 7Department of Psychiatry; 8Department of Medicine, University of Toronto, Toronto, Canada

Received 16 August 2013; revised 18 December 2013; accepted 2 January 2014

Background: Intensive chemotherapy (IC) used to treat acute myeloid leukemia (AML) is associated with toxicity, particularly in older adults. Emerging data suggest that baseline quality of life (QOL) and physical function may predict outcomes in oncology, although data in AML are limited. We investigated the association between baseline QOL and physical function with short-term treatment outcomes in adults and elderly AML patients.

Materials and methods: We conducted a prospective, longitudinal study of adults (age 18+) AML patients undergoing IC. Before starting IC, patients completed the European Organisation for the Research and Treatment of Cancer (EORTC) 30-item questionnaire (QLQ-C30) and Functional Assessment of Cancer Therapy Fatigue subscale (FACT-Fatigue) in addition to physical function tests (grip strength, timed chair stands, 2-min walk test). Outcomes included 60-day mortality, intensive care unit (ICU) admission and achievement of complete remission (CR). Logistic regression was carried out to evaluate each outcome.

*Correspondence to: Dr Shabbir M.H. Alibhai, Department of Medicine, University Health Network, 200 Elizabeth Street, Room EN14-214, Toronto, ON, Canada, M5G 2C4. Tel: +1-416-414-30-5125; Fax: +1-416-596-5826; E-mail: shabbir.alibhai@uhn.ca

© The Author 2014. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oup.com.
introduction

Acute myeloid leukemia (AML) is a malignant blood disorder that primarily affects older adults [1]. Although outcomes have improved over time [2], the prognosis remains considerably worse in older adults due to both host- and disease-specific factors [1].

Intensive chemotherapy (IC), the main curative treatment of AML, is associated with multiple short-term toxic effects including physical deconditioning, declines in quality of life (QOL), increased fatigue and mortality, particularly in older adults [3, 4]. Although complete remission (CR) can be achieved in 75–90% of younger patients who receive IC, fewer older adults (50–60%) attain CR [1]. In addition, older adults who receive IC have greater toxicity than younger adults [including prolonged hospitalization, increased risk of infection, higher rates of intensive care unit (ICU) admission and treatment-related mortality] [5–7]. Furthermore, the rate of relapse remains high and long-term survival is poor among older adults [1].

Although pre-treatment risk stratification is becoming increasingly sophisticated with the use of cytogenetic, molecular and other genetic information [1], selecting the optimal treatment remains challenging, particularly for older adults. Given the toxicity of AML treatment, being able to better predict short-term and long-term outcomes remains an important area of research.

Preliminary data in AML populations suggest that baseline (pre-treatment) QOL and/or objective physical function tests may predict outcomes such as long-term survival [8]. If confirmed, these measures may provide valuable information beyond conventional disease characteristics to aid treatment decision-making, particularly in older adults. However, most literature in the AML population has focused on conventional disease characteristics as predictive factors, including age, performance status, comorbidity, blood parameters (platelet count, blast percentage, haemoglobin etc.) and chromosomal karyotype [5–7]. The purpose of this study is to investigate if baseline QOL and physical function predict short-term treatment outcomes, including 60-day mortality, ICU admission and remission status during IC in both older (60+ years) and younger (18–59 years) patients with AML.

materials and methods

study design

This prospective, longitudinal cohort study was conducted at the Princess Margaret Cancer Centre in Toronto, a tertiary care AML referral and treatment centre. All study procedures were approved by the Institutional Research Ethics Board.

subject recruitment

Potentially eligible participants were identified by treating haematologists or by reviewing patient admissions. Inclusion criteria were: newly diagnosed AML initiating IC, ability to provide written informed consent and fluency in English or having both a translator and questionnaires available in the patient’s first language. Exclusion criteria included: another active malignancy, prior chemotherapy (within 2 years of AML diagnosis) and life expectancy of <1 month (as determined by the physician).

Patients were recruited before or within 3 days of starting IC, which consisted of daunorubicin (60 mg/m²/day) for 3 days and cytarabine (200 mg/m²/day, 100 mg/m²/day for patients ≥60 years) as a continuous infusion for 7 days. Patients achieving CR then received two cycles of consolidation therapy as described previously [9]. Participants with significant left ventricular dysfunction received amsacrine instead of daunorubicin.

objectives

Our primary objective was to determine whether baseline QOL and physical function predicted short-term treatment outcomes, including 60-day mortality, ICU admission and remission status after IC in adult patients with AML. Our secondary objective was to determine whether there were age differences between older and younger patients among predictors of the same short-term outcomes.

baseline, predictor and outcome assessments

At the baseline assessment, both patient-reported outcomes as well as objective physical function were assessed. Additional measures included sociodemographic (age, sex, smoking history etc.) and disease information (cytogenetics, relevant haematology and biochemistry, performance status, comorbidities, medications etc.). Details regarding all measures are described in our previous work [9].

patient-reported outcomes. We assessed QOL using the European Organisation for the Research and Treatment of Cancer (EORTC) 30-item questionnaire (QLQ-C30) and fatigue with both the Functional Assessment of Cancer Therapy Fatigue subscale (FACT-F) and a global single-item fatigue measure from the Edmonton Symptom Assessment Scale. The QLQ-C30 includes five domains (physical, role, emotional, social and cognitive functioning) and a global QOL measure.

physical function tests. Three objective tests were used to assess various aspects of physical function and fitness. The 2-min walk test (2-MWT) was used to assess functional endurance. Grip strength, measured with a Jamar

Results: Of the 239 patients (median age 57.5 years), 56.7% were male and median Charlson comorbidity score was 0. Sixty-day mortality, ICU admission and CR occurred in 9 (3.7%), 15 (6.3%) and 167 (69.9%) patients, respectively. Using univariate regression, neither QOL nor physical function at presentation was predictive of 60-day mortality (all P > 0.05), whereas ICU admission (P < 0.001) and remission status at 30 days (P = 0.007) were. Fatigue (P = 0.004) and role functioning (P = 0.003) were predictors of ICU admission; QOL and physical function were not. A higher Charlson score predicted ICU admission (P = 0.01) and remission status (P = 0.002). The cytogenetic risk group was associated with achievement of CR (P = 0.02); QOL and physical function were not (all P > 0.05). Findings were similar when patients age 60+ were examined. Relationships between fatigue and role functioning with ICU admission deserve further exploration.

Conclusions: Baseline QOL and physical function tests in this prospective study were not associated with short-term mortality, ICU admission or achievement of CR after the first cycle of chemotherapy.

Key words: quality of life, physical function, fatigue, acute myeloid leukemia, short-term mortality, elderly
outcome measures. Mortality was assessed up to 60 days from the start of chemotherapy. ICU admission was documented during the IC admission period. Remission status was determined using the standard criteria [10] following a bone marrow biopsy at ~day 28.

statistical analyses
Descriptive statistics and univariate comparisons among age groups are reported as means with standard deviations for continuous variables and compared using the Student’s t-test. Continuous variables that were not normally distributed are reported as medians with interquartile ranges. Categorical data are reported as proportions and were compared using Fisher’s exact test.

To examine baseline QOL and physical function as predictors of outcomes, we used univariate logistic regression. A P-value of 0.05 was considered significant for all comparisons. Where there were a sufficient number of outcomes, multivariable logistic regression was carried out using forward stepwise selection with a P-value of <0.05 in univariate analyses. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

sensitivity analysis for missing data
In order to assess the impact of missing baseline data on outcomes, a sensitivity analysis was performed. Any patient who was unable to complete a physical function test due to fatigue or illness was assigned a score equal to the median score of the lowest (worst) decile of scores from the patient’s age group at that particular visit and for that specific test [11, 12].

results
baseline characteristics
Among 393 potentially eligible patients (224 under 60 years, 169 age 60 or older), we were able to approach 355. Of these, 24 were no longer eligible (primarily due to language barrier) and 92 declined (57 under 60 years, 35 age 60 or older). A total of 239 eligible patients (64% of eligible; 142 under 60 years, 97 age 60 or older) were enrolled between May 2008 and March 2012. Baseline sociodemographic and disease characteristics are presented in supplementary Table S1, available at Annals of Oncology online. The median age of all participants was 57.5 years. The majority of participants were male (56.1%) and had good baseline performance status (ECOG score 0 or 1; 82.4%) along with no significant comorbidity [mean (SD) Charlson score, 0.31 (0.6)].

There were no statistical differences between older and younger patients in either global QOL or fatigue at the time of diagnosis. However, both social and emotional functioning were significantly better in older patients (P = 0.004 and P = 0.02, respectively) (supplementary Table S2, available at Annals of Oncology online). Younger patients performed better on most physical measures at baseline when compared with older adults, although none of the comparisons were statistically significant (supplementary Table S2, available at Annals of Oncology online).

60-day mortality
Supplementary Table S3, available at Annals of Oncology online, outlines 30- and 60-day mortality data for all patients. Nine patients (3.7%) died within 60 days of starting IC, 5 patients ≥60 years (5.2%) and 4 patients <60 years (2.8%). ICU admission was the most powerful predictor of 60-day mortality; patients admitted to the ICU were 27 times more likely to die within 60 days of treatment initiation (OR 27.5, P < 0.001). Conversely, being in CR at 30 days was associated with lower 60-day mortality (OR 0.11, P = 0.007). Neither global QOL nor physical performance measures were predictive of 60-day mortality (P > 0.05; Table 1). There were too few outcomes for a multivariable analysis.

ICU admission
Fifteen patients (6.2%) were admitted to the ICU during their admission for IC, of whom 3 were ≥60 years (3.1%) and 12 were <60 years (8.5%) (supplementary Table S3, available at Annals of Oncology online). Criteria for ICU admission did not change over time in our centre, and did not differ by age group. A higher Charlson score at baseline was a significant predictor of ICU admission (P = 0.01). In addition, role functioning and FACT-fatigue at baseline were also predictive of ICU admission (P = 0.003 and P = 0.02, respectively). However, other QOL domains and physical performance measures were not associated with ICU admission (Table 1). There were too few outcomes for a multivariable analysis.

remission status
Most patients (69.9%) achieved CR at the end of the first cycle of treatment (65% older versus 73% younger patients) (supplementary Table S3, available at Annals of Oncology online). In univariate analyses, bone marrow blast percentage (P = 0.009) at presentation, secondary AML (P = 0.002), unfavourable cytogenetics (P = 0.02) and a higher Charlson score (P = 0.002) were significantly associated with a lower likelihood of achieving CR (Table 1). Among QOL variables, only emotional functioning was a significant predictor of remission status (P = 0.04); no physical performance measure was predictive (all P > 0.05) (Table 1). In multivariate analyses, after adjusting for age, bone marrow blast percentage, Charlson comorbidity score, cytogenetic risk group and secondary AML, emotional functioning remained a significant predictor of remission status (P = 0.026) (supplementary Table S4, available at Annals of Oncology online).

age-stratified comparisons
We examined whether there were differences between older and younger patients in rates of 60-day mortality, ICU admission and CR status. Results across these outcomes were consistent among both cohorts (supplementary Table S3, available at Annals of Oncology online). In addition, we examined whether QOL or physical function tests were predictive of outcomes in the older cohort. These results were identical to findings for the entire cohort (data not shown).

impact of missing data and sensitivity analysis
Fifteen patients were unable to complete the global QOL and FACT-F assessment (6.3%) at baseline due to illness or fatigue, while 14 (7%), 53 (22.2%) and 57 (24.7%) patients were unable
### Table 1. Univariate predictors of 60-day mortality, ICU admission and remission status

<table>
<thead>
<tr>
<th>Variable</th>
<th>60-day mortality [OR (95% CI)]</th>
<th>P-value</th>
<th>ICU admission [OR (95% CI)]</th>
<th>P-value</th>
<th>Remission status [OR (95% CI)]</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.29 (0.96–2.21)</td>
<td>0.35</td>
<td>0.84 (0.58–1.22)</td>
<td>0.36</td>
<td>0.83 (0.67–1.03)</td>
<td>0.08</td>
</tr>
<tr>
<td>Age group (&lt;60 versus ≥60)</td>
<td>0.53 (0.14–2.04)</td>
<td>0.36</td>
<td>2.89 (0.79–10.5)</td>
<td>0.11</td>
<td>1.47 (0.85–2.58)</td>
<td>0.17</td>
</tr>
<tr>
<td>Gender (F versus M)</td>
<td>1.02 (0.27–3.90)</td>
<td>0.97</td>
<td>0.62 (0.21–1.87)</td>
<td>0.39</td>
<td>1.46 (0.83–2.57)</td>
<td>0.18</td>
</tr>
<tr>
<td>BMI</td>
<td>1.04 (0.96–1.14)</td>
<td>0.33</td>
<td>1.01 (0.94–1.10)</td>
<td>0.73</td>
<td>0.99 (0.96–1.04)</td>
<td>0.90</td>
</tr>
<tr>
<td>Race (white versus others)</td>
<td>0.82 (0.20–3.38)</td>
<td>0.79</td>
<td>1.15 (0.35–3.34)</td>
<td>0.82</td>
<td>0.73 (0.39–1.37)</td>
<td>0.33</td>
</tr>
<tr>
<td>Smoking status (ever versus non-smoker)</td>
<td>0.28 (0.06–1.41)</td>
<td>0.12</td>
<td>1.21 (0.42–3.44)</td>
<td>0.73</td>
<td>1.19 (0.68–2.08)</td>
<td>0.52</td>
</tr>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 versus 0</td>
<td>0.81 (0.17–3.74)</td>
<td>0.79</td>
<td>0.53 (0.13–2.19)</td>
<td>0.38</td>
<td>1.24 (0.67–2.31)</td>
<td>0.48</td>
</tr>
<tr>
<td>2+ versus 0</td>
<td>1.24 (0.22–7.03)</td>
<td>0.81</td>
<td>2.69 (0.82–8.89)</td>
<td>0.10</td>
<td>0.81 (0.38–1.73)</td>
<td>0.58</td>
</tr>
<tr>
<td>Karnofsky score (per 10 point)</td>
<td>0.92 (0.59–1.43)</td>
<td>0.72</td>
<td>0.72 (0.52–0.99)</td>
<td>0.05</td>
<td>1.11 (0.92–1.34)</td>
<td>0.27</td>
</tr>
<tr>
<td>Charlson score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 versus 0</td>
<td>3.07 (0.56–16.7)</td>
<td>0.19</td>
<td>4.76 (1.45–15.5)</td>
<td>0.01</td>
<td>0.81 (0.33–1.98)</td>
<td>0.64</td>
</tr>
<tr>
<td>2+ versus 0</td>
<td>3.35 (0.61–18.3)</td>
<td>0.16</td>
<td>0.87 (0.11–7.18)</td>
<td>0.89</td>
<td>0.26 (0.11–0.62)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetic risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favourable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
to complete physical performance measures (grip strength, chair stands and 2-MWT, respectively). The proportion of missing data was similar between older and younger patients (all $P > 0.05$, data not shown).

After imputation of data, our findings were similar to our primary analysis. Neither global QOL nor physical performance measures were predictive of 60-day mortality, ICU admission or CR (all $P > 0.05$, data not shown). Imputed baseline role functioning and FACT-F scores remained predictive of ICU admission ($P = 0.004$ and $P = 0.03$, respectively) and better emotional functioning remained predictive of remission status ($P = 0.048$).

**Discussion**

We examined whether baseline QOL and physical function predicted short-term treatment outcomes, including 60-day mortality, ICU admission and remission status during IC in older (60+ years) and younger (18–59 years) patients with AML. We demonstrated that poor risk cytogenetics, ICU admission and residual disease following initial chemotherapy were all predictive of 60-day mortality. Similarly, patients with greater comorbidity at baseline were more likely to be admitted to the ICU and less likely to achieve remission at 30 days. Of the QOL variables, role functioning and fatigue were predictive of ICU admission, whereas emotional functioning was predictive of remission status. None of the other QOL variables or physical function measures were associated with outcomes. Finally, although older adults who undergo IC typically experience greater toxicity, similar results were observed between both age groups in our study. This may be due to the careful selection of older adults who undergo IC at our institution.

This is the first study of its kind to examine the predictive ability of QOL and physical function on short-term outcomes among patients with AML. It is also unique in that it encompasses both younger and older patient populations. Although we did not observe relationships with some of the measures that we initially thought may be predictive, several limitations of the current study may influence these outcomes. We did not collect self-reported health status or physical activity before diagnosis. Moreover, the physical performance measures we used may not have been sufficiently sensitive. More vigorous fitness-based testing may be more predictive (e.g. VO$_2$ max). Some patients were not enrolled until 3 days after starting IC, which may have affected their baseline QOL and physical function scores. More importantly, there is no simple way to distinguish whether poor QOL or physical function at baseline is due to pre-existing comorbidities or a consequence of AML. Finally, despite a relatively large sample size overall, few people died within 60 days or were admitted to ICU during IC, decreasing our power to examine these outcomes, particularly in multivariable models.

Of interest, a recent paper by Klepin et al. [13] examined whether elements of geriatric assessment were predictive of outcomes in an elderly AML cohort undergoing IC. Among 74 patients, the authors found that poor performance on the Short Physical Performance Battery (SPPB) but not grip strength was predictive of overall survival. The SPPB includes three physical performance measures—gait speed, 5 timed chair stands and a test of balance. While it is possible that the SPPB is a better measure of physical function than the measures we included (2-MWT, 10 timed chair stands), our study differs in several important ways from Klepin et al. We included both younger and older adults and examined short-term mortality, whereas Klepin et al. included only patients age 60 or older and examined overall survival at a median of 11 months. A second study, by Oliva et al. [8], demonstrated that QOL was independently predictive of long-term survival in an elderly AML cohort treated predominantly with palliative approaches. Thus, further studies involving these QOL and physical function predictors in different AML populations are warranted.

We observed relatively low 30-day and 60-day mortality rates in both age groups, similar to trends observed in other datasets [14]. Despite this, we did find that comorbidity was associated with 60-day mortality, which has been noted previously [15]. We also found that ICU admission was associated with 60-day mortality. We could not find any other studies that examined risk factors for ICU admission among AML patients undergoing induction chemotherapy, although multiple studies have examined this outcome in this group of patients [16–18].

Our findings regarding predictors of achieving CR are similar to other studies, in that unfavourable cytogenetics and higher
initial bone marrow blast percentage were associated with a lower likelihood of achieving CR [5, 6]. We also found that emotional functioning was an independent predictor of remission status after adjusting for cytogenetics, bone marrow blast percentage and comorbidity. This is a novel finding, although its clinical implications are uncertain at this time. Various studies in oncology have examined whether personality style or other psychosocial variables are associated with survival, with varying results, but we are not aware of any prior study that has examined this issue in AML. Given our limitations above, this finding should be replicated before further attempts are undertaken to understand the causes and possible clinical implications.

Another interesting finding in our study was that fatigue and role functioning at baseline were predictive of ICU admission. While it is tempting to speculate as to why this may be, we had too few ICU admissions to justify a multivariable analysis. In addition, we have previously shown that fatigue correlates not only with most aspects of QOL in AML patients but also with specific inflammatory cytokines, several of which were also correlated with the presence of infection [19]. Thus, on the one hand, fatigue may be a marker of illness severity. On the other hand, it may not be independently predictive of ICU admission once other clinical factors are adjusted for. Our finding does warrant confirmation in future larger studies as it may have clinical implications (e.g. closer clinical monitoring).

This work, and the work by Oliva et al. [8] and Klepin et al. [13], provides a foundation from which additional research can continue to identify specific non-traditional measures such as patient-reported outcomes, geriatric assessment parameters and physical performance measures that are easily measurable at the bedside and may enhance our ability to predict outcomes, particularly among older adults with AML, thereby aiding clinical decision-making in this challenging disease.

acknowledgements
The authors gratefully acknowledge the patients and families who enrolled in the study, volunteers and research students of Dr Alibhai’s Research Team and the Princess Margaret Cancer Centre, University Health Network, and the Sunnybrook Odette Cancer Center, University of Toronto.

disclosure
The authors have declared no conflicts of interest.

references