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Comorbidity, age, and mortality among adults treated intensively for acute myeloid leukemia (AML)

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ABSTRACT

Introduction: Our goal was to characterize comorbidities among adults receiving intensive therapy for AML, and investigate their association with outcomes.
Methods: We retrospectively analyzed 277 consecutive patients with newly diagnosed AML treated intensively at the Comprehensive Cancer Center of Wake Forest University from 2002 to 2009. Pretreatment comorbidities were identified by *ICD-9* codes and chart review. Comorbidity burden (modified Charlson Comorbidity Index [CCI]) and specific conditions were analyzed individually. Outcomes were overall survival (OS), remission, and 30-day mortality. Covariates included age, gender, cytogenetic characteristics, hemoglobin, white cell count, lactate dehydrogenase, body mass index, and insurance type. Cox proportional hazards models were used to evaluate OS; logistic regression was used for remission and 30-day mortality.
Results: In this series, 144 patients were ≥60 years old (median age 70 years, median survival 8.7 months) and 133 were <60 years (median age 47 years, median survival 23.1 months). Older patients had a higher comorbidity burden (CCI ≥ 1 58% versus 26%, $P < 0.001$). Prevalent comorbid conditions differed by age (diabetes 19.2% versus 7.5%; cardiovascular disease 12.5% versus 4.5%, for older versus younger patients, respectively). The CCI was not independently associated with OS or 30-day mortality in either age group. Among older patients, diabetes was associated with higher 30-day mortality (33.3% vs. 12.0% in diabetic vs. non-diabetic patients, p = 0.006). Controlling for age, cytogenetic characteristics and other comorbidities, the presence of diabetes increased the odds of 30-day mortality by 4.9 (CI 1.6–15.2) times.
Discussion: Diabetes is adversely associated with 30-day survival in older AML patients receiving intensive therapy.

Abbreviations: AML, Acute myeloid leukemia; BMI, Body mass index; CCI, Charlson Comorbidity Index; CR, Complete remission; CI, Confidence interval; HCT-CI, Hematopoietic Cell Transplantation–Comorbidity Index; OR, Odds ratio; OS, Overall survival; mCCI, modified Charlson Comorbidity Index.

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1. Introduction

Acute myeloid leukemia (AML) is a disease of older adults with a median age of onset of 68–72 years (1). Older age is consistently associated with worse survival and higher treatment-associated morbidity (2,3,4). Poor outcomes for older adults with AML are attributable to both tumor biology and age-related patient characteristics that decrease treatment tolerance (4,5). Identifying measurable patient characteristics that contribute to suboptimal outcomes among older adults can help individualize pre-treatment assessment and inform supportive management of those patients. One area of particular interest is the assessment of comorbidities, because they are common among older patients and can influence treatment decision making and toxicity risk.

Older patients with AML often have a substantial comorbidity burden (6–11). Prevalence estimates of at least one major comorbid condition range from 30% to 70% in most studies. Furthermore, many studies of older adults with AML show a relationship between greater comorbidity burden (measured by Charlson Comorbidity Index [CCI] or Hematopoietic Stem Cell Transplantation Comorbidity Index [HCT-CI]) and worse outcomes including lower remission rates, higher risk of 30-day mortality and worse -(OS) (6–9,12,13). However, not all studies have confirmed these relationships (10,14,15). Comparisons across studies are limited due to differences in patient selection and treatments received. In addition, accounting for patient characteristics such as physical function may attenuate some of the independent effects of comorbidity burden on outcomes (10). Finally, measuring comorbidity burden alone may miss the prognostic importance of specific conditions. Understanding which comorbidities have a greater influence on treatment tolerance would better inform management decisions for individual patients than comorbidity burden scores alone.

The aims of this study were to characterize comorbidity by age within an intensively treated AML population and to investigate associations among comorbidities and OS, remission rates, and 30-day mortality.

2. Methods

2.1. Study Population

Using electronic medical records, we retrospectively analyzed the characteristics of consecutive patients who met the following inclusion criteria: newly diagnosed AML, receipt of intensive induction treatment at the Comprehensive Cancer Center of Wake Forest University between 2002 and 2009, and age > 18 years. Patients with acute promyelocytic leukemia (APL) or those receiving "less intense" regimens (including hypomethylating agents, palliative chemotherapy, or no treatment) were excluded from the study. Regimens of chemotherapy were deemed "intense" if they included cytarabine and anthracycline. Patients were also excluded if they received prior chemotherapy for another hematological malignancy or if the date of induction was not recorded. This study was approved by the Institutional Review Board of Wake Forest School of Medicine.

2.2. Measures

2.2.1. Predictor Variables

Comorbidity data were collected using *ICD-9* codes and chart review from data available in the electronic medical record on or before the date of induction chemotherapy. Comorbidity burden was measured using the modified CCI, excluding AML (8,16). Individual comorbidities evaluated (and their respective *ICD-9* codes) were myocardial infarction (410-412), congestive heart failure (398–398.99, 402–402.91, 428–428.43), peripheral vascular disease (440–447.9), dementia (290–291.5, 294–294.9), cerebrovascular accident (430–433.99, 435–435.9), chronic obstructive pulmonary disease (491–493.22), connective tissue disease (710–710.9, 714–714.33, 725), peptic ulcer disease (531–534.91), liver disease (571–573.39, 070–070.9, 570–572.4), hemiplegia (342–342.12, 434–434.11, 436, 437–437.7), renal disease (403–404.93, 580–586), diabetes (250–250.93), and malignancy (140–195.8, 196–199.2).

2.2.2. Covariates

We collected baseline data on age (stratified at the time of diagnosis as age ≥60 vs. <60 years(4)), gender, body mass index (BMI), race, type of insurance, cytogenetic risk stratification score (17), and type and date of induction chemotherapy. We also collected laboratory data, including glucose, hemoglobin, bilirubin, white blood cell count, creatinine, and lactate dehydrogenase, from the date of presentation for induction therapy in the hospital.

2.2.3. Outcomes

Outcomes were OS from date of induction chemotherapy initiation, treatment response as defined by complete remission, and 30-day mortality. Complete remission (CR) was defined as absolute neutrophil count >1000/microliter (mcl), platelets ≥100,000/mcl, and no residual or extra medullary disease. Complete remission with incomplete count recovery (CRi) was defined as <5% bone marrow blasts and transfusion independence with persistent cytopenia with either an absolute neutrophil count <1000/mcl or platelets <100,000/mcl (18). For analyses, the remission outcome included CR + CRi. Thirty-day mortality was calculated from date of initiation of induction chemotherapy. The cause of death among those who experienced 30-day mortality was abstracted from the medical record. For exploratory analyses, the cause of death was defined as the primary precipitant of multi-system organ failure/death as attributed in the discharge summary.

2.2.4. Statistical Analysis

Data were stratified by age group (<60, ≥60 years), and descriptive statistics were calculated to examine differences between the strata. Categorical variables were compared using a chi-squared test and a t-test was used to compare continuous measures. Some of the measures required a log transformation in order to meet the normality assumption. Cox proportional hazards models were used for bivariate analysis as well as the fully adjusted model to estimate survival. For all analyses, comorbidity burden (CCI) was categorized as none vs. 1 or more based on the distribution of comorbidity scores. We also performed analysis of prevalent individual conditions including diabetes mellitus, renal disease, myocardial