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Prior cytopenia predicts worse clinical outcome in acute myeloid leukemia

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ABSTRACT

The prognosis of acute myeloid leukemia (AML) is influenced by both disease-intrinsic and patient-related factors. In particular, AML following myelodysplastic syndrome (MDS) (AML with myelodysplasia-related changes, AML-MRC) has a poor prognosis. We hypothesized that patients with cytopenias prior to AML, but no known prior MDS, may share biologic features with AML-MRC. We evaluated 140 AML patients without prior MDS who had complete blood count (CBC) data available 6–36 months prior to their diagnosis. Cytopenia, defined as clinically unexplained thrombocytopenia or macrocytic anemia, was present in 29/140 (21%) patients. Compared to non-cytopenic patients, AML patients with prior cytopenia were older and more often met morphologic or cytogenetic criteria for AML-MRC. Prior cytopenia was associated with shorter survival in patients with intermediate-risk cytogenetics (median OS 4.2 versus 24.1 months, $p < 0.0001$), but not in patients with adverse-risk cytogenetics (median OS 4.4 versus 6.0 months, $p = 0.57$). Prior thrombocytopenia, but not macrocytic anemia, was significantly associated with shorter overall survival ($p = 0.01$) independent of treatment approach, karyotype risk, and age on multivariable analysis. Our data suggest that AML patients with prior cytopenias have features similar to AML-MRC, and in particular support the use of prior unexplained thrombocytopenia as an independent marker of high-risk disease.

1. Introduction

Acute myeloid leukemia (AML) is a clonal myeloid neoplasm that is generally defined by the presence of ≥20% myeloid blasts in the peripheral blood or bone marrow. The clinical prognosis of the disease is influenced by both the intrinsic tumor biology (currently determined using the karyotype and mutational status of specific oncogenes) as well as patient-specific factors such as age and performance status. History of an antecedent myeloid neoplasm, such as a myelodysplastic syndrome (MDS), or prior exposure to cytotoxic agents, are associated with adverse prognosis, and as a result are distinguished as specific AML entities in the 2008 WHO Classification of myeloid neoplasms [1]. A substantial proportion of patients with AML have had antecedent MDS, a preleukemic clonal neoplasm characterized by cytopenia(s) and morphologic dysplasia of hematopoietic cells. Such cases are diagnosed as AML with myelodysplasia-related changes (AML-MRC), an AML subtype associated with a particularly poor prognosis [2]. This diagnosis can also be made in patients lacking a history of MDS but demonstrating MDS-associated cytogenetic abnormalities or significant morphologic dysplasia (at least 50% of cells in two or more lineages) [1,3]; however, the prognostic relevance of multilineage dysplasia alone, without an established preceding diagnosis of MDS, remains controversial [4,5]. Nevertheless, AML-MRC does appear to have a molecular mutation pattern that is distinct from that of de novo AML [6]. Patients who do not fulfill WHO criteria for AML-MRC or other defined subtypes are diagnosed with AML, not otherwise specified (AML-NOS), which captures a heterogeneous group of disorders with variable prognosis [7].

Current WHO Classification criteria require an established pathologic diagnosis of MDS in order to classify a case as AML-MRC, in the absence of specific cytogenetic abnormalities or multilineage dysplasia. However, patients typically are only diagnosed with MDS when they present with cytopenias, which then prompt a diagnostic bone marrow biopsy. Cytopenic patients with elevated

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MCV and red cell distribution width (RDW) are more likely to be diagnosed with MDS than patients who have normocytic anemia, thrombocytopenia, or leukopenia [8]. In patients diagnosed with MDS, macrocytic anemia is present in 80–85%, thrombocytopenia in 30–45%, and neutropenia in 40%, and therefore unexplained anemia, particularly when macrocytic, should prompt consideration of an MDS diagnosis [9]. Anemia is relatively common in elderly patients, seen in an estimated 10% of adults over 65 years, and approximately one third remain unexplained after clinical workup. Of those, approximately 15% have concomitant macrocytosis, thrombocytopenia or leukopenia, raising the possibility of an underlying MDS [10–12], which may prompt bone marrow biopsy to confirm or exclude the diagnosis [13,14]. In one retrospective series reviewing bone marrow biopsies performed for unexplained cytopenias, approximately 30% of patients were diagnosed with probable or definite MDS; the incidence of MDS in cytopenic patients who do not undergo bone marrow sampling is not known [8].

Some investigators have used persistent (>6 months) cytopenias (in addition to a pathologically confirmed MDS) as indicative of an "antecedent hematologic disorder" for the purposes of clinical trials [15]. To our knowledge, however, there are no prior studies examining the features of AML developing in patients with antecedent cytopenias who have no prior history of hematologic malignancy as a way to identify patients who may have adverse outcome similar to AML-MRC. In the current study, we hypothesized that unexplained cytopenias, defined as macrocytic anemia or prior thrombocytopenia, prior to an AML diagnosis may represent an undiagnosed MDS in many of these patients, and therefore may be associated with clinical and prognostic features similar to AML-MRC.

2. Materials and methods

We searched the pathology records from two hospitals (Massachusetts General Hospital [MGH] from 2003 to 2013 and Brigham and Women's Hospital [BWH] from 2007 to 2012) for adult (age > 18) patients with a new diagnosis of AML. 622 (345 from BWH, 277 from MGH) patients were identified and their electronic medical records reviewed to identify patients with complete blood count (CBC) data available between 6 and 36 months prior to diagnosis. We used data from 177 de novo AML patients from MGH lacking a prior CBC as a control group. Patients with macrocytic anemia or thrombocytopenia due to Vitamin B12 or folate deficiency, aplastic anemia, liver failure, renal failure, or treatment-responsive immune thrombocytopenic purpura were excluded. For patients with CBCs performed at the time of a surgical procedure, pre-operative values were used. Patient characteristics including age, co-morbidities at the time of CBC draw, and reason for CBC testing were recorded. A prior cytopenia was defined as macrocytic anemia or thrombocytopenia (outside each hospital's normal reference range for hematocrit, MCV, and platelet count, according to patient gender); neutropenia was not included as a criterion since WBC differentials were not available for a large proportion of patients. Clinical data at the time of AML diagnosis included CBC, ECOG performance status, and AML therapy. AML therapies were categorized as supportive care only (including blood product and growth factor support and/or hydroxyurea), low-intensity chemotherapies (including hypomethylating agents), and induction chemotherapy. Patients were also categorized according to whether they underwent allogeneic hematopoietic stem cell transplantation. Overall survival (OS) was defined as the time from AML diagnosis until patient death, with censoring at last known alive date during survival analysis.

All AML cases were diagnosed according to the 2008 WHO Classification, as well as by the FAB system when data concerning myeloperoxidase expression and monocytic features were available. Slides were reviewed for all AML cases with morphologic dysplasia described in the pathology report; these cases were classified as AML-MRC if they fulfilled WHO Classification morphologic criteria [1]. Karyotypes were reported using the International System for Human Cytogenetic Nomenclature and cytogenetic risk group stratification was based on the United Kingdom Medical Research Council trials (UKMRC) classification [16]. The presence of *FLT3* and/or *NPM1* mutations was recorded when available.

Fisher's exact test and Mann–Whitney tests were used to compare categorical and continuous variables between groups, respectively. Overall survival (OS) and disease-specific survival (DSS) from diagnosis was estimated using the method of Kaplan and Meier; the log-rank test was used to compare OS between groups. For DSS, patients who died of causes unrelated to AML were censored at the time of death. Univariate Cox proportional hazards regression was performed to assess the impact of variables on OS, and values significant at the 0.20 level were included in multivariable Cox proportional hazards regression. A 2-sided p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Clinical features of patient groups

A total of 140 AML patients with prior CBC data were identified (85 from MGH and 55 from BWH). The circumstances in which the CBC was obtained were as follows: evaluation of a medical condition (52), routine primary care visit (39), surgical procedure (19), emergency room visit/trauma (10), and obstetric visit/delivery (2). The reason for the visit was unknown or undocumented for 18 patients. Overall, according to the prior CBC, 59 patients (42%) had prior anemia (including 15 [11%] with macrocytic anemia), 20 (14%) had prior thrombocytopenia, and 33 (24%) had prior leukopenia. Twenty-nine patients (21%) had macrocytic anemia and/or thrombocytopenia, and were considered the "AML with prior cytopenia group" (AML-cytopenic) for the purposes of this study. The remaining 111 patients comprised the AML-non-cytopenic group, which lacked macrocytic anemia or thrombocytopenia; this group included 20 patients with leukopenia and 33 patients with normocytic or microcytic anemia. At the time of the CBC prior to AML diagnosis, AML-cytopenic patients were older than AML-non-cytopenic patients ($p = 0.001$), but had no significant difference in co-morbidities that may be associated with macrocytic anemia or thrombocytopenia (Table 1). There was no significant difference in the time from prior CBC to AML diagnosis between the AML-cytopenic and AML-non-cytopenic groups (median 10 versus 12 months, respectively; $p = 0.36$). In addition, 177 de novo AML patients from MGH diagnosed during the same time period but lacking a prior CBC were identified as a control group. Compared to the AML-non-cytopenic patients, the AML patients without any prior CBC were younger (median age 58 versus 65 years, $p = 0.007$), but showed no difference in gender distribution ($p = 0.33$), ECOG performance status ($p = 0.32$), hematocrit ($p = 0.85$), white blood count ($p = 0.33$), or platelet count ($p = 0.89$) at the time of AML presentation.

3.2. Cytogenetic and molecular genetic abnormalities

There was a significant difference in the distribution of cytogenetic abnormalities at AML diagnosis between these two groups ($p = 0.02$, Table 2). Cytogenetically favorable risk AML was not observed in any of the AML-cytopenic patients, but comprised 17% of the AML-non-cytopenic patients. Conversely, adverse risk karyotypes were more frequent in AML-cytopenic (38%) compared to AML-non-cytopenic (20%) patients. Chromosomal aberrations in adverse-risk cases were similar between AML-cytopenic and AML-non-cytopenic groups: −7/del(7q) (3/11 AML-cytopenic versus 10/22 AML-non-cytopenic, $p = 0.46$), −5/del(5q) (7/11 AML-cytopenic versus 15/22 AML-non-cytopenic, $p = 1.0$), complex (≥3 chromosomal abnormalities) karyotype (8/11 AML-cytopenic versus 18/22 AML-non-cytopenic, $p = 0.66$), and number of cytogenetic abnormalities (median 6 [range 1–12] for AML-cytopenic and median 7 [range 1–15] for AML-non-cytopenic, $p = 0.50$). Full karyotypes of all 29 AML-cytopenic patients are shown in Supplemental Table 1. Among those with molecular testing, 18/59 (30%) AML-non-cytopenic patients and 3/11 (27%) AML-cytopenic patients had *FLT3-ITD* mutations, while 18/57 (32%) AML-non-cytopenic and 5/11 (45%) AML-cytopenic patient had *NPM1* mutations. There was no difference the distribution of AML cytogenetic risk groupings ($p = 0.49$) between AML-non-cytopenic patients and the 177 AML patients without any prior CBC.