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A cytogenetic model predicts relapse risk and survival in patients with acute myeloid leukemia undergoing hematopoietic stem cell transplantation in morphologic complete remission

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ABSTRACT

Up to 30% of patients with acute myeloid leukemia (AML) and abnormal cytogenetics have persistent cytogenetic abnormalities (pCytAbnl) at morphologic complete remission (mCR). We hypothesized that the prognostic significance of pCytAbnl in patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) in mCR varies with cytogenetic risk group. We analyzed the data on 118 patients with AML and abnormal cytogenetics who underwent HSCT in mCR, and developed a risk stratification model based on pCytAbnl and cytogenetic risk group. The model distinguished three groups of patients ($P < 0.01$) with distinct outcomes: the group with pCytAbnl and unfavorable risk cytogenetics ($n = 25$) had the shortest median time to relapse (TTR; 5 months), relapse-free survival (RFS; 3 months), and overall survival (OS; 7 months). The group with favorable/intermediate risk cytogenetics and without pCytAbnl ($n = 43$) had the longest median TTR (not reached), RFS (57 months), and OS (57 months). The group with pCytAbnl and favorable/intermediate risk cytogenetics, or, without pCytAbnl but with unfavorable risk cytogenetics ($n = 50$) experienced intermediate TTR (18 months), RFS (9 months), and OS (18 months). In conclusion, a cytogenetic risk model identifies patients with AML in mCR with distinct rates of relapse and survival following HSCT.

1. Introduction

Acute myeloid leukemia (AML) relapses after allogeneic hematopoietic stem cell transplantation (HSCT) in 30–35% of patients. Relapse occurs typically within the first 6 months posttransplantation and portends a dismal prognosis, with a median post-relapse overall survival (OS) of 3–6 months [1–3]. Chemotherapy and donor lymphocyte infusion provide only limited post-relapse median OS of less than 3 months [1]. Although second HSCT may offer durable remissions with 5-year OS rates approaching 30% [4], only a minority of patients are eligible to receive a second transplant. Given the currently poor prognosis of patients with relapsed AML following HSCT, risk-stratification of patients based on pretransplantation characteristics could help identify those patients who will not benefit from HSCT or guide the implementation of strategies to reduce the risk of posttransplant relapse.

Approximately 10–30% of patients with an abnormal karyotype at the time of diagnosis of AML have persistent cytogenetic abnormalities (pCytAbnl) at morphologic complete remission (mCR) [5–8]. In a non-transplant setting these patients have higher overall mortality and relapse risk compared to those without pCytAbnl [7], but the significance of pCytAbnl at the time of mCR in patients who undergo HSCT has been inconsistent and not clearly defined. Considering that unfavorable cytogenetics at diagnosis is associated with higher relapse rates and shorter relapse-free survival (RFS) after HSCT [9], we hypothesized that the prognostic significance of pCytAbnl in patients undergoing HSCT in mCR varies with the cytogenetic risk group. Using a large cohort of patients with AML and abnormal cytogenetics at diagnosis who underwent HSCT in mCR, we develop a simple risk stratification model that enables us to delineate patients with distinct rates of relapse, RFS, and OS.

2. Materials and methods

2.1. Patients

By reviewing our computerized database, we identified consecutive adult patients (age ≥18 years) with AML with cytogenetic abnormalities at initial diagnosis, who underwent HSCT while in morphological CR between January 2009 and July 2013. The institutional review board of the Washington University School of

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Medicine approved this retrospective analysis. The majority of patients were treated on clinical trials. All patients gave written informed consent before undergoing HSCT.

2.2. Cytogenetic analysis

All samples were analyzed by standard cytogenetic techniques in our institution. At least 20 metaphases from the bone marrow were required to define a karyotype as normal. For cytogenetically abnormal samples, analyses with fewer than 20 metaphases were also acceptable. Following the International System for Human Cytogenetic Nomenclature [10], a cytogenetic abnormality was considered clonal when at least two metaphases had the same aberration in case of structural abnormalities or trisomies. The requirement for definition of clonal monosomies was their presence in at least three metaphases. Cytogenetic risk group was defined according to the guidelines of the Southwest Oncology Group and Eastern Cooperative Oncology Group [11].

2.3. Stem cell transplantation

Patients who received myeloablative or reduced-intensity conditioning regimens were included. Standard mobilization protocols and apheresis techniques were used for the procurement of donor bone marrow or G-CSF-primed peripheral blood stem cells. Transplants from a matched sibling were favored over those from unrelated donors or HLA-haploidentical siblings. The most frequently used GvHD prophylaxis regimens were tacrolimus plus methotrexate, with or without mycophenolate mofetil. Tacrolimus was dose-adjusted to maintain blood levels of 5–15 ng/dL during the first 100 days posttransplant and then tapered, as clinically indicated. Methotrexate was most commonly given at a dose of 10 mg/m^2 on day +1 and 7.5 mg/m^2 on days +3 and +6. Filgrastim was administered subcutaneously daily beginning on day +7 posttransplant or otherwise if dictated by the protocol. Filgrastim was discontinued once the absolute neutrophil count recovered to more than 1.5×10^9/L for 2 consecutive days. Cytomegalovirus (CMV) surveillance consisted of weekly screening by polymerase chain reaction (PCR), with preemptive use of ganciclovir or foscarnet if new positivity or rising titers were discovered.

2.4. Definitions

pCytAbnl was defined as cytogenetic abnormalities detected by fluorescence *in situ* hybridization or metaphase cytogenetics at mCR that were present in the clone at the time of diagnosis of AML. According to the criteria reported by the International Working Group [12], mCR was defined as <5% blast cells, no Auer rods, and no cluster of blast cells on the bone marrow analysis, as well as no evidence of extramedullary leukemia. A cytogenetic abnormality at the time of diagnosis of AML that did not disappear on a bone marrow biopsy done performed within 2 months preceding HSCT (and before conditioning) and in mCR was considered persistent. A monosomal karyotype (MK) was defined as at least two autosomal monosomies or a single autosomal monosomy in the presence of one or more structural cytogenetic abnormalities [13]. Relapse was defined as ≥5% blasts in the bone marrow or development of extramedullary leukemia. Bone marrow analysis was performed on days +30 and +100 posttransplant, and every 3–6 months thereafter. For RFS, patients were considered to experience failures at the time of relapse or death from any cause. For OS, the event was death from any cause. Time to relapse (TTR) was measured from the day of transplantation.

2.5. Statistical analyses

Unadjusted probabilities of OS and RFS were estimated using the Kaplan–Meier method. All outcomes were treated as time-to-event points. OS was measured from the date of transplantation until the date of death and censored on the date of last follow up if alive. RFS was measured from the date of transplantation and censored on the date of last follow up if alive and in remission. Variables with a normal distribution are presented as mean ± standard deviation (SD), and those with a skewed distribution as median (standard error of the mean; SEM). Analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL), and a P value of <0.05 was considered statistically significant.

3. Results

A total of 118 patients (age 51 ± 14 years, 58% males) met the inclusion criteria. AML was therapy-related in 21 (31%) patients, 15 (71%) of whom had a known myelodysplastic syndrome that

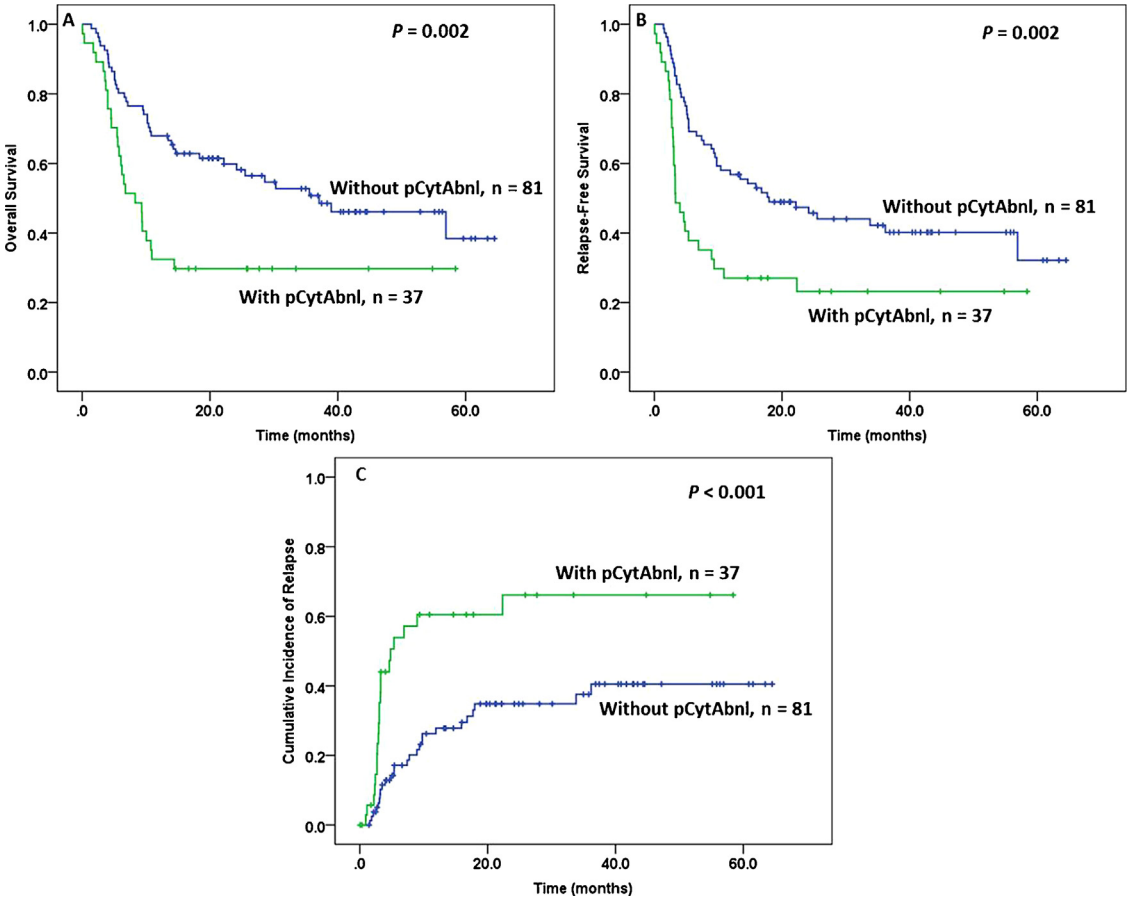

Fig. 1. Overall survival (A), relapse-free survival (B), and cumulative incidence of relapse (C) in patients with and without persistence of cytogenetic abnormalities (pCytAbnl).