A Prognostic Model of Therapy-Related Myelodysplastic Syndrome for Predicting Survival and Transformation to Acute Myeloid Leukemia

Alfonso Quintás-Cardama,[1] Naval Daver,[1] Hawk Kim,[2] Courtney Dinardo,[1] Elias Jabbour,[1] Tapan Kadia,[1] Gautam Borthakur,[1] Sherry Pierce,[1] Jianqin Shan,[1] Marylou Cardenas-Turanzas,[1] Jorge Cortes,[1] Farhad Ravandi,[1] William Wierda,[1] Zeev Estrov,[1] Stefan Faderl,[1] Yue Wei,[1] Hagop Kantarjian,[1] Guillermo Garcia-Manero[1]

Abstract

We propose a prognostic model specific to patients with therapy-related myelodysplastic syndrome (t-MDS). This model identifies three distinct survival groups among patients with t-MDS. The model is applicable in routine clinical practice and might facilitate the development of risk-adapted therapeutic strategies.

Introduction/Background: We evaluated the characteristics of a cohort of patients with myelodysplastic syndrome (MDS) related to therapy (t-MDS) to create a prognostic model. **Patients and Methods:** We identified 281 patients with MDS who had received previous chemotherapy and/or radiotherapy for previous malignancy. Potential prognostic factors were determined using univariate and multivariate analyses. **Results:** Multivariate Cox regression analysis identified 7 factors that independently predicted short survival in t-MDS: age $\geq$ 65 years (hazard ratio [HR], 1.63), Eastern Cooperative Oncology Group performance status 2-4 (HR, 1.86), poor cytogenetics (-7 and/or complex; HR, 2.47), World Health Organization MDS subtype (RARs or RAEB-1/2; HR, 1.92), hemoglobin ($<$ 11 g/dL; HR, 2.24), platelets ($< 50 \times 10^9$/dL; HR, 2.01), and transfusion dependency (HR, 1.59). These risk factors were used to create a prognostic model that segregated patients into 3 groups with distinct median overall survival: good (0-2 risk factors; 34 months), intermediate (3-4 risk factors; 12 months), and poor (5-7 risk factors; 5 months) ($P < .001$) and 1-year leukemia-free survival (96%, 84%, and 72%, respectively, $P = .003$). This model also identified distinct survival groups according to t-MDS therapy. **Conclusion:** In summary, we devised a prognostic model specifically for patients with t-MDS that predicted overall survival and leukemia-free survival. This model might facilitate the development of risk-adapted therapeutic strategies.

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Introduction

The term, myelodysplastic syndrome (MDS), refers to a heterogeneous group of hematopoietic clonal disorders characterized by deregulation of apoptosis, dysplastic features in hematopoietic precursors, peripheral blood cytopenias, and an increased tendency to transformation to acute myeloid leukemia (AML).[1,2] A significant fraction of patients with MDS have a previous history of an antecedent malignancy (hematologic or otherwise) treated with chemotherapy and/or radiotherapy.[3-6] Therapy-related MDS (t-MDS) is included in the therapy-related myeloid neoplasms category of the 2008 World Health Organization (WHO) classification.[7] The clinical course of t-MDS is customarily progressive and associated

Alfonso Quintás-Cardama and Naval Daver contributed equally to this work.

[1]Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, Houston, TX
[2]Division of Hematology-Oncology, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

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Address for correspondence: Guillermo Garcia-Manero, MD, Department of Leukemia, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Unit 428, Houston, TX 77030
Fax: 713-794-4297; e-mail contact: ggarciam@mdanderson.org

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with high resistance to standard chemotherapeutic approaches used for MDS arising de novo.[3,5,6] Cases of t-MDS have been reported after chemotherapy for acute lymphoblastic leukemia, Hodgkin and non-Hodgkin lymphoma, sarcoma, testicular cancer, and adenocarcinoma of the breast, among others.[8-11] The median latency interval from therapy of the primary malignancy and the diagnosis of t-MDS or therapy-related AML (t-AML) has been reported to be 64 months for patients with an antecedent hematologic malignancy and 55 months for those with primary solid tumors.[12] Alkylating agents, through the formation of crosslinks and DNA monoadducts, and topoisomerase II inhibitors, through the induction of chromosomal breakages, are the chemotherapeutic agents more frequently associated with t-MDS. The use of alkylating agents or topoisomerase II inhibitors has been associated with t-MDS after a latency of 3 to 5 years and 0.5 to 3 years, respectively.[13,14]

Recurrent chromosomal abnormalities are present in 40% to 70% of patients with de novo MDS at diagnosis.[15] However, those are present in 95% of patients with t-MDS, frequently in the context of complex karyotypes.[12] Frequent chromosomal abnormalities in patients with t-MDS after treatment with alkylating agents include -5/del(5q), -7/del(7q), and/or +8, whereas translocations involving 11q23 or 21q22, and t(17;19)(q22;12), have been frequently reported in patients with previous exposure to topoisomerase II inhibitors. Of note, these abnormalities are frequently associated with a multidrug-resistant phenotype and are also commonly found in patients with AML.[15,16]

The inherent biological heterogeneity of MDS makes it necessary to develop prognostic systems to predict long-term outcomes. Several classification systems and prognostic models are currently available to segregate patients with MDS into subsets with distinct prognosis, including the French-American-British (FAB),[1] the WHO,[17] and the International Prognostic Scoring System (IPSS) classifications.[18] The IPSS, which classifies patients based on the presence of chromosomal abnormalities assessed using conventional cytogenetics, bone marrow blast burden, and the number of cytopenias is currently the most widely accepted prognostic system for patients with MDS. However, the IPSS score is neither applicable to patients with chronic myelomonocytic leukemia (CMML) with white blood cell (WBC) count $> 12 \times 10^9$/L, nor to those with t-MDS. To overcome these limitations, novel prognostic models have been developed, such as the WHO classification-based Prognostic Scoring System (WPSS),[19] a prognostic model specifically for patients with low-risk MDS,[20] and a new global prognostic model that predicts the risk of patients with MDS in a dynamic fashion at any time during the course of therapy.[21] Although several independent predictors of survival (ie, marrow blast percentage and cytogenetics),[20] are common to all these prognostic systems, others are system-specific. For instance, the main prognostic factors of WPSS are transfusion dependency, the WHO subtype of MDS, and chromosomal abnormalities and in the global prognostic model developed by our group, factors such as blasts, hemoglobin, cytogenetics, age, and platelet count are particularly important. However, the development of all these systems were largely based on cohorts of patients with de novo MDS. Thus, the utility of such models to prognosticate survival has not been validated in a large cohort of patients with t-MDS. Furthermore, most available risk analyses have been performed using mixed cohorts of patients including those with t-MDS and t-AML. On these grounds, we interrogated a large cohort of patients with t-MDS to validate the factors that independently predicted for survival and transformation to AML. The resulting prognostic system could be used as a tool for risk-stratification purposes in t-MDS.

Patients and Methods

Patient Selection

This analysis focused on t-MDS arising in patients with an antecedent malignancy that required previous chemotherapy or radiation therapy. Therefore, patients with MDS and an antecedent malignancy who had not received chemotherapy or radiotherapy were excluded. Patients with $\geq$ 20% blasts were classified as having AML, according to WHO criteria, and they were also excluded. Basic demographic data were obtained from the M.D. Anderson Cancer Center (MDACC) MDS database. All patients with t-MDS included in this analysis were diagnosed and treated at MDACC between 1998 and 2007. Medical records were reviewed for confirmation of diagnosis of a previous malignancy, details related to the therapy for such previous malignancy, and t-MDS directed therapy.

Categorization of MDS Therapy

Therapies received by patients with t-MDS were grouped as follows: growth factor and/or supportive care; standard cytotoxic chemotherapy; noncytotoxic therapy (hypomethylating agents, thalidomide/lenalidomide, investigational drugs, and immunosuppressive agents); and allogeneic hematopoietic stem cell transplantation (SCT). If a patient had received more than 1 treatment category, the patient was ascribed to the more intensive treatment category.

Analysis of Risk Factors

Risk factors analyzed for survival included hepatomegaly (present vs. absent), chromosome alterations (5q-, 20q-, Y-, normal vs. others), MDS subtype according to the WHO classification (Refractory anemia (RA), Refractory cytopenia with multilineage dysplasia (RCMD), MDS unknown (MDSu) vs. others), hemoglobin, platelet counts, WBC counts, marrow blast percentage, time from previous treatment to MDS, number of lines of therapy for previous malignancies, serum albumin, serum β-2 microglobulin, serum creatinine, Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs. $\geq$ 2), age, sex, previous therapy (chemotherapy vs. radiotherapy only), previous malignancies (hematological vs. solid tumors), previous transfusion, previous lymphoma (lymphoma vs. nonlymphoma), previous hematopoietic SCT (autologous vs. allogeneic vs. none) and serum ferritin level ($\leq$ 600 vs. $>$ 600 ng/mL). Risk factor comparisons used median values, adjusted with respect to statistical differences. Risk group classification based on cytogenetics was identified and categorized on the basic analysis of survival by every chromosomal alteration.

Statistical Analysis

For continuous variables, data are reported as medians and range. For nominal variables, data are reported as the number of patients (with percentage in parentheses), if not specified otherwise. Continuous variables were dichotomized and coded into binary