Outcome of azacitidine treatment in patients with therapy-related myeloid neoplasms with assessment of prognostic risk stratification models

Vu H. Duong, Jeffrey E. Lancet, Ezzideen Alrawi, Najla H. Al-Ali, Janelle Perkins, Teresa Field, Pearlie K. Epling-Burnette, Ling Zhang, Alan F. List, Rami S. Komrokji*

H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

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ABSTRACT

Azacitidine's efficacy in therapy-related myeloid neoplasms (t-MN) has not been well-studied. In our retrospective review of 84 t-MN patients treated with azacitidine, median overall survival (OS) was 14.5 months and overall response rate was 43%, including 11% complete remission, 4% marrow complete remission, and 11% partial remission. In patients who underwent allogeneic transplant (25%), median OS was 19.2 versus 12.8 months ($P = 0.023$) for those who did not. Response rates were comparable to those reported for de novo myelodysplastic syndrome. When we analyzed outcomes according to five scoring systems, only the Global MD Anderson Risk Model predicted survival with statistical significance.

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1. Introduction

The 2008 World Health Organization (WHO)-defined therapy-related myeloid neoplasms (t-MN) span a continuum of clinically similar hematologic malignancies, including therapy-related myelodysplastic syndrome (t-MDS), therapy-related acute myelogenous leukemia (t-AML), and t-MDS/myeloproliferative neoplasms [1]. These diseases arise as complications from prior radiation and/or chemotherapy for prior neoplastic or non-neoplastic disorders, often leading to characteristic cytogenetic abnormalities. Prognosis is generally poor when compared to their de novo counterparts due to several factors, including poor risk karyotype, older age, poor performance status, number of comorbidities, and resistance to conventional cytotoxic chemotherapies. One series reported a median overall survival of 8 months after diagnosis and less than 10% five-year survival rate [2].

t-MDS accounts for up to 20% of patients with MDS, and patients may present at any age [3–6]. The clinical presentation varies by agent, with a latency of 5–7 years and frequent chromosome 5 and 7 abnormalities with prior exposure to alkylating agents and a latency of months to years with 11q23 abnormalities more common after topoisomerase II inhibitors.

Azacitidine, a DNA methyltransferase inhibitor, is currently the preferred agent for patients with MDS, particularly those with higher-risk International Prognostic Scoring System (IPSS) score owing to two large, randomized clinical trials [7,8]. The first trial, conducted by the Cancer and Leukemia Group B, compared azacitidine to best supportive care, reporting significantly higher overall response rates and a trend toward overall survival benefit, leading to its approval by the U.S. Food and Drug Administration. Six percent of patients received prior radiotherapy and 14% received prior chemotherapy; however, results for patients with t-MDS were not reported separately [8]. The landmark AZA-001 study demonstrated increased time to leukemic transformation and an overall survival benefit with azacitidine compared to three different conventional care regimens in patients with higher-risk MDS, oligoblastic AML, and CMML, but patients with t-MN were excluded from the trial [7].

A recently presented model for t-MDS by Quintás-Cardama and colleagues identified and validated seven prognostic factors that predict survival: age at least 65 years, ECOG performance status greater than 1, monosomy 7 or complex cytogenetics, WHO MDS subtype of refractory anemia with ringed sideroblasts (RARS) or refractory anemia with excess blasts (RAEB)-1 or -2, hemoglobin less than 11 g/dL, platelets less than 50,000 $(\mu L)^{-1}$, and transfusion dependency [9]. Patients in the good (0–2 factors), intermediate (3–4 factors), and poor (5–7 factors) risk categories had median survival of 34, 12, and 5 months, respectively. However, only a fraction of patients were treated with hypomethylating agent-based therapy, and the number of patients treated specifically with azacitidine was not reported [9].

* Corresponding author at: Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Drive, FOB-3, Room 3117, Tampa, FL 33612, USA.
Tel.: +1 813 745 4291; fax: +1 813 745 5617.
E-mail address: rami.komrokji@moffitt.org (R.S. Komrokji).

Outcomes using azacitidine in patients with t-MN have not been well-documented in the literature. One study of a compassionate-use azacitidine program reported a 43% overall response rate and a median overall survival of 9.2 months in a subset of patients with t-MDS [10], and one recent retrospective study of patients with t-MN documented a 42% overall response rate and a 21-month median survival [11]. Otherwise, the data are limited to small retrospective series with limited analyses [12,13] and case reports [14,15]. In this retrospective study, we investigated the outcomes of t-MN patients treated with azacitidine at the Moffitt Cancer Center.

2. Methods

This was a retrospective review of t-MN patients treated at the Moffitt Cancer Center with azacitidine. Patients were identified through the Moffitt MDS database, individual charts were reviewed, and clinical data were extracted. Patients were required to have a diagnosis of MDS, chronic myelomonocytic leukemia, or AML with less than 30% bone marrow blasts (refractory anemia with excess blasts in transformation by French–American–British criteria) confirmed by bone marrow biopsy. Patients were required to have a history of treatment with chemotherapy or radiation therapy for any hematologic malignancy or solid tumor and must have received at least one dose of azacitidine. Patients who received radioactive iodine were included, but patients treated with brachytherapy alone were excluded from the analysis. Data collected and recorded included age, gender, complete blood counts, percentage of marrow blasts, prior malignancies and therapies, cytogenetics, performance status, transfusion requirements, dates and cycles of azacitidine therapy, and dates of progression and death, among others. The study was reviewed and approved by both the Scientific Review Committee and Institutional Review Board.

The primary objective of the study was to evaluate the overall survival in this cohort of patients. Survival was defined as the time period beginning from day 1 of the first cycle of azacitidine until the date of death. Secondary endpoints included evaluating best response to azacitidine according to the International Working Group 2006 criteria [16], feasibility of allogeneic transplant, validation of the t-MDS risk score, and survival according to IPSS [17], revised International Prognostic Scoring System (rIPSS) [18], WHO Classification-Based Prognostic Scoring System (WPSS) [19], and Global MD Anderson Risk Score [20].

Disease status was defined by the WHO classification system. Cytogenetics were categorized as favorable (normal, -y, 5q-, or 20q-), unfavorable (-7, 3 or more abnormalities), or intermediate (all others). Response to azacitidine was evaluated utilizing the International Working Group 2006 criteria. The IPSS, rIPSS, WPSS, and the Global MD Anderson Scoring System were used to evaluate risk. The newly proposed t-MDS risk model from MD Anderson was also applied. Patients were assigned one point for each of the following disease characteristics: age at least 65 years, ECOG performance status higher than 1, monosomy 7 or complex cytogenetics, WHO MDS subtype of RARS or RAEB-1 or -2, hemoglobin less than 11 g/dL, platelets less than 50,000 $(\mu L)^{-1}$, and transfusion dependency. Patients were categorized as low risk if 0–2 factors were present, intermediate risk if 3–4 factors were present, and high risk if 5 or more factors were present [9]. Descriptive statistics were used for baseline characteristics and responses, and the Kaplan–Meier method with log-rank test was used to evaluate survival and for comparison between groups. For each risk model, patients with insufficient data to assign a risk score were excluded from the survival analysis. In addition, if the risk model as originally developed and validated did not include patients with AML or CMML, these patients were also excluded from our analysis of that particular model. All statistical analyses were conducted using SPSS software, version 20.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Patient characteristics

Between July 2004 and December 2011, 84 t-MN patients were identified who were treated at the Moffitt Cancer Center with azacitidine. Baseline characteristics of these patients are shown in Table 1. The median age of the cohort was 65 years, with a slight male predominance (56%). The vast majority (88%) was Caucasian, and 72% had an ECOG performance status of 1 or better. Fifty-two percent had a previous hematologic malignancy, 43% had a history of a solid tumor, and 5% had a history of both hematologic malignancy and solid tumor. Chemotherapy was previously administered in 51% of patients, radiation in 12% of patients, and both chemotherapy and radiation in 37%. Half of the patients had either RAEB-1 (27%) or RAEB-2 (23%), and 8% had AML at the time of diagnosis by WHO criteria. By IPSS score, 18 (21%) had

Table 1
Baseline patient characteristics (N = 84).

Characteristics	N (%)
Median age, years (range)	65 (36–84)
Gender	
Male	47 (56%)
Female	37 (44%)
Race	
Caucasian	74 (88%)
Other	8 (10%)
Unknown	2 (2%)
ECOG performance status	
0	12 (14%)
1	49 (58%)
≥2	23 (27%)
Prior malignancy	
Hematologic malignancy	44 (52%)
Solid tumor	36 (43%)
Both	4 (5%)
Prior therapy	
Chemotherapy	43 (51%)
Radiation	10 (12%)
Both	31 (37%)
WHO subtype	
RA	2 (2%)
RARS	4 (5%)
RCMD	27 (32%)
RAEB-1	23 (27%)
RAEB-2	19 (23%)
CMML	1 (1%)
AML (≤30% blasts)	7 (8%)
Missing	1 (1%)
Karyotype	
Favorable	12 (14%)
Intermediate	9 (11%)
Unfavorable	60 (71%)
Missing	3 (4%)
RBC transfusion dependence	71 (85%)
Median number of cycles of azacitidine (range)	4.5 (1–21)
IPSS	
Low	1 (1%)
Intermediate-1	18 (21%)
Intermediate-2	49 (58%)
High	13 (16%)
Missing	3 (4%)
rIPSS	
Very Good	1 (1%)
Good	8 (10%)
Intermediate	7 (8%)
Poor	12 (14%)
Very Poor	48 (57%)
Missing	8 (10%)
WPSS	
Low	3 (4%)
Intermediate	5 (7%)
High	34 (45%)
Very High	30 (39%)
Missing	4 (5%)
MD Anderson risk score	
Low	1 (1%)
Intermediate-1	7 (8%)
Intermediate-2	23 (27%)
High	53 (63%)
Missing	0

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; IPSS, International Prognostic Scoring System; rIPSS, revised IPSS; RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; WPSS, WHO Classification-Based Prognostic Scoring System.

an intermediate-1 score, 49 (58%) had an intermediate-2 score, 13 (16%) had a high-risk score, and 3 (4%) had insufficient data. When the rIPSS was used, 1 (1%) had a very good score, 8 (10%) had a good score, 7 (8%) had an intermediate score, 12 (14%) had a poor score, 48 (57%) had a very poor score, and 8 (10%) had insufficient data to calculate a score. When the WPSS was applied to the 76 patients without AML, 3 (4%) had a low score, 5 (7%) had an