Treatment of Acute Myelogenous Leukemia With Outpatient Azacitidine

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BACKGROUND. Patients older than 55 years of age with acute myelogenous leukemia (AML) are less likely to achieve complete remission and more likely to experience toxicity with conventional induction chemotherapy than younger patients. Azacitidine administered in the outpatient setting is well tolerated and can induce complete hematological remission in patients with myelodysplastic syndromes (MDS). At higher doses, azacitidine has activity in AML.

METHODS. Twenty patients were retrospectively identified who had been treated with azacitidine with bone marrow blast counts between 21 and 38%. Patients with blast counts up to 29% were initially treated as MDS, but by WHO now meet criteria for AML. Patients with blast counts over 29% were treated with azacitidine after being deemed poor candidates for induction chemotherapy. Azacitidine 75 mg/m^2/day was administered subcutaneously for 7 days every 4 weeks, which was defined as 1 cycle.

RESULTS. The overall response rate was 60% (12/20): complete response (CR; $n = 4$; 20%); partial response (PR; $n = 5$; 25%); hematologic improvement (HI; $n = 3$; 15%). The median survival of responders was 15+ months compared with 2.5 months for nonresponders ($P = .009$). During therapy, responders had an Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 0. The most common toxic event was infection ($n = 8$). Four patients were hospitalized during the first cycle of treatment.

CONCLUSIONS. Azacitidine administered in the outpatient setting can induce remission in AML. The therapy is well tolerated and might be an alternative for patients unlikely to tolerate standard induction chemotherapy. ***Cancer* 2006;107: 1839–43.** © *2006 American Cancer Society.*

KEYWORDS: azacitidine, acute myeloid leukemia, AML, chemotherapy.

Induction therapy for acute myeloid leukemia (AML) traditionally requires intensive chemotherapy with an anthracycline compound and cytarabine. Remission rates of up to 70% are seen in patients less than 60 years of age and from 30% to 50% in older patients.[1–3] This treatment is associated with significant morbidity, often necessitating prolonged hospitalization. In addition, patients over age 60 generally experience significantly greater treatment-related morbidity and mortality compared with younger patients. In general, 1/3 of patients succumb to complications of treatment, 1/3 remain leukemic, and 1/3 enter remission. Despite consolidation therapy, most patients experience recurrence within months. Additionally, older patients often have concurrent medical conditions that are exacerbated by chemotherapy. As a result, patients with poor performance status or with significant comorbid conditions are often not treated with traditional induction therapy, but rather with supportive care using antibiotics and transfusion. This approach generally results in limited

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survival (3–6 months), often with a poor quality of life.[2] New therapeutic options are needed for such patients.

Azacitidine is a derivative of the nucleoside cytosine. It is a cell cycle-specific cytotoxic agent and has multiple effects on DNA metabolism. Azacitidine is incorporated into DNA and produces a marked decrease in the activity of DNA methyltransferase.[4] In vitro exposure of an erythroleukemic cell line to azacitidine resulted in induction of differentiation.[5] Presumably this effect was related to hypomethylation of the DNA. Earlier clinical studies demonstrated activity of high-dose intravenous azacitidine in patients with AML. A review of these trials reveals that of 171 patients, 18% achieved a complete response (CR) with an overall response rate of 27%.[6] Remission was achieved in an average of 46 days with a median duration of 112 days.[6] Although these results were promising, clinical utility was limited due to extensive toxicity.

Several trials have demonstrated the effectiveness of this drug when given at a lower dose by the subcutaneous route of administration to patients with myelodysplastic syndrome (MDS).[7,8] A randomized Phase III trial showed clinical benefit in approximately 60% of patients and led to approval of azacitidine for the treatment of MDS.[7]

We present a retrospective analysis of our experience with the use of azacitidine as first-line therapy for patients with AML, as defined by the World Health Organization (WHO) classification (blasts $\geq$20%).[9]

MATERIALS AND METHODS

Patients

Patients were enrolled in the azacitidine compassionate use program through the National Cancer Institute (NCI) from 1996 to 2001. Twelve patients with bone marrow (BM) blast counts up to 29%, with a mean age of 66 years (range, 44–80), were previously judged by the French-American-British (FAB) classification as having refractory anemia with excess blasts in transformation (RAEB-t).[10] Under the newer WHO classification, these patients meet criteria for AML. An additional 8 patients had greater than 29% blasts in the marrow, with a mean age of 71 years (range, 58–79), and were deemed to be poor candidates for standard induction therapy. Nine of the patients were reported in our original series of patients with MDS as having RAEB-t.[8]

Methods

All patients received azacitidine at a dose of 75 mg/m^2/day for 7 consecutive days via subcutaneous injection. This cycle was repeated every 28 days for as long as therapy was tolerated and a response was maintained. The first injection was given in the outpatient setting under observation. Subsequent injections were self-administered at home. An oral 5-HT3 antagonist was given as an antiemetic before each injection. Compliance was assessed verbally and by counting syringes that were returned for disposal. Performance status was assessed by Eastern Cooperative Oncology Group (ECOG) criteria.

Response Criteria

Response was assessed by NCI definition of response in AML or by International Working Group (IWG) criteria for hematologic improvement in MDS.[11–13] CR was defined as BM cellularity greater than 20%, BM blast cell count less than 5%, and no Auer rods detected for at least 4 weeks. In addition, the peripheral blood (PB) contained an absolute neutrophil count $\geq 1.5 \times 10^9$/L, platelets $> 100 \times 10^9$/L, and no PB blasts for at least 4 weeks. Partial response (PR) required that all the criteria for CR were met except BM blast cells were between 5% and 25% with no detectable Auer rods or $\leq$5% BM blast cells in the presence of Auer rods. Patients not meeting these definitions of response were further assessed for hematologic improvement (HI) using the IWG criteria for MDS. Progressive disease (PD) was defined as a >50% increase in BM blast cells. Overall response rate (ORR) was defined as the sum of CR, PR, and HI. Transfusion independence was defined as an interval of at least 2 months without transfusion.

RESULTS

Patient Characteristics

The patient characteristics are depicted in Table 1. Twenty patients were analyzed (15 males, 5 females; mean age, 68 years, age range, 44–80 years). Thirteen patients presented with leukopenia, 10 of whom had no circulating blasts. Six had high white blood counts (range, 27.1–79.4 k/mcl) with 6% to 70% circulating blasts. Twelve patients had bone marrow blasts in the range of 20% to 29% and 8 patients had blasts >29%. Thirteen had cytogenetic abnormalities. Eleven of 20 patients were solely red blood cell (PRBC) transfusion-dependent, 7 were both PRBC and platelet transfusion-dependent, and 2 patients were independent of transfusion at the start of treatment. Prior therapy included transfusion ($n = 18$), growth factor support in patients previously defined as having MDS ($n = 5$), vitamin B12 and folic acid ($n = 3$), and chemotherapy (low dose for MDS) ($n = 2$). ECOG performance status was 1 or better for all patients before treatment initiation. The average time from diagnosis to starting azacitidine therapy was 11 months with a range of 1 to 48 months. Two patients underwent allogeneic hematopoietic stem cell

TABLE 1
Patient Characteristics and Response to Therapy

Patient no.	Age/sex	Peripheral blood WBC/blasts	Marrow blasts (%)	Cytogenetics at diagnosis	Type of response	Time to response, months	Response duration, months	Survival, months
1	74/M	39.1/25%	38	46, XY	CR	3	13	24
2	79/M	1.6/3%	37	Complex	PR	2	1	10
3	77/M	1.0/0%	30	46, XY	PR	2	2	10
4	68/F	2.6/2%	30	del (20), add (12)	HI	3	7/11	13
5	79/F	2.8/0%	21	Complex	CR	3	7	14
6	54/F	2.5/16%	28	46, XX	CR	2	6	8
7	44/M	39.5/28%	21	46, XY	CR	5	6	16
8	68/M	1.6/0%	25	46, XY	PR	3	33	36+
9	79/M	4.8/0%	29	46, XY	PR	3	16	18
10	71/M	1.6/0%	25	t(1;3)(p36;q21)	HI	2	2	15
11	80/M	2.3/0%	22	Complex	NR			4
12	77/M	45.8/41%	22	Complex with monosomy 7	NR			2
13	50/F	3.1/0%	23	t(6;9)(p23;q34)	NR			11
14	51/M	1.0/0%	22	Complex	NR			2
15	69/M	3.7/0%	29	46, XY	HI	3	17	18
16	76/F	1.0/0%	53	Complex	PR	3	12	15
17	61/M	27.1/70%	70	Complex	NR			
18	58/M	3.0/0%	32	Complex	NR			
19	78/M	52.2/3%	29	20q-	NR			
20	68/M	79.4/6%	21	17q10	NR			

WBC, white blood cell; CR, complete response; PR, partial response; HI, hematologic improvement; NR, no response.

transplantation (HSCT) after 8 and 14 cycles while still in response. Both died, at Days 76 and 300 after transplant. Their survival, for this study, was calculated up to their transplant date. Dose reductions of 25% were employed in 2 patients due to marked cytopenia after the second and fifth cycle, respectively. The dose was increased to 75 mg/m^2/day after counts improved 2 to 3 cycles later. Dose escalation ranging from 100 to 200 mg/m^2/day was employed in 4 patients who did not respond or who demonstrated progression after an initial response.

TABLE 2
Toxicity Data

Toxic event	Patients (n = 15)
Febrile neutropenia	3
Pneumonia	3
Death due to infection	3
Thrombocytopenia with bleeding	1
Herpes zoster	1
Anorexia	1
Perirectal abscess	1
Rash	1

Toxicity

Toxicity is outlined in Table 2. Mild injection site irritation was a common extramedullary toxicity, but did not result in dose modification or cessation of therapy in any patient. While on therapy, 3 patients experienced neutropenic fever and 3 developed pneumonia. These complications resulted in 3 deaths. Dose reduction was required in 2 patients, 1 due to neutropenia and 1 due to thrombocytopenia. Both patients eventually tolerated full dose after recovery. One patient required discontinuation of therapy due to severe anorexia. Other single toxic events included Herpes zoster, perirectal abcess, and rash.

Four patients required hospitalization during the first cycle of treatment: 2 with febrile neutropenia, 1 with pneumonia, and 1 with a groin pseudoaneurysm due to a coronary catheterization. These complications resulted in 2 deaths before the start of the second cycle. Another of these patients died of disease progression before cycle 2. Overall, 8 patients required hospitalization during treatment, 7 of which were due to infection.

Response to Azacitidine

All patients received at least 1 cycle of azacitidine and were considered evaluable for response. ORR was 60% (12 of 20 patients). CR was achieved in 4 patients (20%), PR in 5 (25%), and HI in 3 (15%). Median time to response was 3 months (range, 2–5 months). The

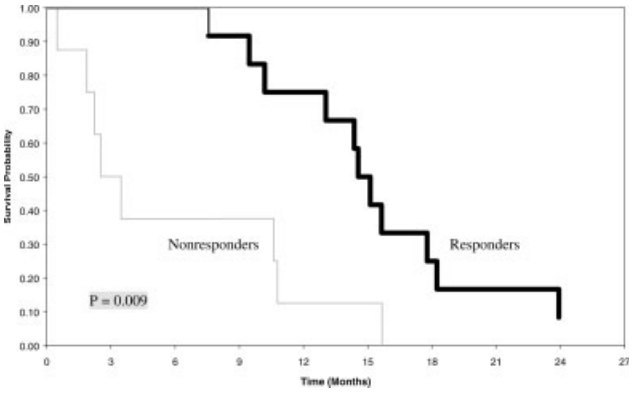

FIGURE 1. Overall survival by response.

TABLE 3
Pretreatment and Posttreatment Hemoglobin and Platelet Counts

Patient no.	Pretreatment, hemoglobin/Platelets	Posttreatment median hemoglobin (range)/ median platelets (range)
1	7.5/21	11.0 (8.8–13.0)/180 (3–237)
2	8.6/31	10.4 (7.9–11.6)/50 (13–174)
3	10.6/29	10.4 (8.1–11.4)/132 (17–300)
4	9.8/9	9.4 (7.4–11.6)/20 (3–51)
5	9.3/40	17.3 (7.2–18.0)/251 (5–574)
6	8.3/247	13.0 (8.3–13.4)/125 (54–287)
7	7.7/19	16.3 (7.0–16.9)/164 (12–269)
8	11.6/66	14.1 (9.0–15.8)/184 (61–351)
9	8.6/70	9.2 (8.2–12.7)/60 (16–143)
10	9.0/85	9.8 (8.8–11.7)/165 (69–232)
15	8.6/9	8.9 (7.8–10.8)/46 (3–74)
16	9.7/45	12.7 (6.8–14.6)/119 (5–279)

median duration of response of patients who responded ($n = 12$) was 8 months (range, 3–33). The median survival of responders was 15+ months (range, 10–36^{+}) compared with 2.5 months for nonresponders ($P = .009$) (Fig. 1). There was no significant difference in survival based on the type of response (CR vs. PR vs. HI). All responders maintained an ECOG performance status of 0–1 throughout treatment. Patients 6 and 7 were taken to allogeneic peripheral blood stem cell transplant during response. Patient 8 achieved a maximal response of PR and continues to receive azacitidine after 36 months of therapy. The 4 patients who received an escalated dose of azacitidine due to PD did not respond to the higher dose.

Eighteen of the patients were transfusion-dependent (11 PRBC and 7 both platelet and PRBC transfusion dependent) at the initiation of azacitidine therapy. Eleven patients became independent of PRBC or platelet transfusion. The pre- and posttreatment hemoglobin and platelet counts of responders are outlined in Table 3.

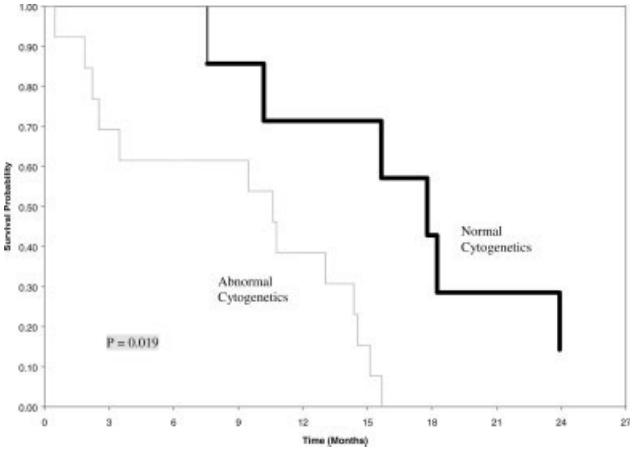

FIGURE 2. Overall survival by cytogenetics.

Cytogenetic study before initiation of therapy revealed a normal karyotype ($n = 7$), simple abnormalities ($n = 5$), and complex abnormalities ($n = 8$). All of the patients with a normal cytogenetic study achieved a response (3 CR, 3 PR, 1 HI). Of those with simple cytogenetic abnormalities, 2 of 5 patients achieved a response (HI). Three of the 8 patients with complex cytogenetics achieved a response (1 CR, 2 PR). Median survival for patients with abnormal cytogenetics was 10.6 months, compared with 17.8 months for patients with normal cytogenetics ($P = .019$) (Fig. 2).

DISCUSSION

Half of all patients with AML are over age 60. Standard induction chemotherapy is associated with high morbidity and mortality in this older population. Despite treatment, only 1/3 of these patients achieve remission, which lasts a few months, even with consolidation therapy. Patients frequently require prolonged hospitalization and many experience worsening of their performance status. Some patients are judged unable to tolerate chemotherapy and are treated with palliative measures. These patients typically experience a poor quality of life and limited survival.

Azacitidine is a hypomethylating agent that is thought to induce cellular differentiation. The drug has been studied extensively in MDS and is now widely used. High-dose intravenous (IV) azacitidine had been studied in AML, but its use was limited due to toxicity. In a single study, low-dose IV azacitidine was ineffective in 11 patients; however, 9/11 patients had recurrent or refractory disease and only 2 cycles of therapy were administered.[14] Silverman et al.[7] demonstrated the efficacy of azacitidine in MDS in a large CALGB study. This CALGB study included 16 patients with RAEB-t and 10 with AML. Of these 26 patients approximately 60%

achieved a response (CR + PR + improvement). Median duration of response was reported as 15 months. Two additional CALGB studies utilizing azacitidine demonstrated response rates of 48% and 32% in patients meeting WHO criteria for AML.[15]

We retrospectively analyzed the response to outpatient subcutaneous azacitidine therapy in newly diagnosed, previously untreated patients with AML. Response was observed in 60% of patients with an average survival in responders of 15+ months, similar to the findings of Silverman et al.[7,15] Toxicity was largely manageable in the outpatient setting and ECOG performance status in responders remained 1 or less throughout therapy. Eight patients were hospitalized for complications during treatment. Only 4 patients required hospitalization during cycle 1. In contrast, treatment with traditional chemotherapy requires hospitalization of all patients during infusion and usually for an additional 2–4 weeks for complications while pancytopenic.

The clinical heterogeneity of acute leukemia progression is well recognized and might have influenced these results. A relevant entity is smoldering leukemia, which is recognized but not clearly defined. Smoldering AML has been described as having slower clinical progression and longer survival than overt AML.[16,17] The majority of our patients ($n = 14$) presented with normal or low blood WBC, many ($n = 11$) having no peripheral blood blasts. It is conceivable that some of the patients in our study had smoldering leukemia, which as a selection bias might improve overall survival.

In conclusion, azacitidine appears to be active in the treatment of older patients with AML who are poor candidates for standard induction chemotherapy. This therapy appears tolerable in poor-risk patients and can be managed largely in an outpatient setting. Whereas our sample size was small, cytogenetic study might have prognostic significance for therapy with azacitidine. A prospective Phase II study is planned to document the activity and toxicity of azacitidine in older patients with AML.

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