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Maintenance Therapy with Decitabine after Allogeneic Stem Cell Transplantation for Acute Myelogenous Leukemia and Myelodysplastic Syndrome

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A B S T R A C T

Decitabine is a hypomethylating agent that irreversibly inhibits DNA methyltransferase I, inducing leukemic differentiation and re-expression of epigenetically silenced putative tumor antigens. We assessed safety and efficacy of decitabine maintenance after allogeneic transplantation for acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS). Decitabine maintenance may help eradicate minimal residual disease, decrease the incidence of graft-versus-host disease (GVHD), and facilitate a graft-versus-leukemia effect by enhancing the effect of T regulatory lymphocytes. Patients with AML/MDS in complete remission (CR) after allotransplantation started decitabine between day +50 and +100. We investigated 4 decitabine doses in cohorts of 4 patients: 5, 7.5, 10, and 15 mg/m^2/day × 5 days every 6 weeks, for a maximum 8 cycles. The maximum tolerated dose (MTD) was defined as the maximum dose at which ≤ 25% of people experience dose-limiting toxicities during the first cycle of treatment. Twenty-four patients were enrolled and 22 were evaluable. All 4 dose levels were completed and no MTD was reached. Overall, decitabine maintenance was well tolerated. Grade 3 and 4 hematological toxicities were experienced by 75% of patients, including all patients treated at the highest dose level. Nine patients completed all 8 cycles and 8 of them remain in CR. Nine patients died from relapse (n = 4), infectious complications (n = 3), and GVHD (n = 2). Most occurrences of acute GVHD were mild and resolved without interruption of treatment; 1 patient died of acute gut GVHD. Decitabine maintenance did not clearly impact the rate of chronic GVHD. Although there was a trend of increased FOXP3 expression, results were not statistically significant. In conclusion, decitabine maintenance is associated with acceptable toxicities when given in the post-allotransplantation setting. Although the MTD was not reached, the dose of 10 mg/m^2 for 5 days every 6 weeks appeared to be the optimal dose rather than 15 mg/m^2, where most hematological toxicities occurred.

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (alloHSCT) is a potentially curative therapy for patients with high-risk acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Over the past decade, we have witnessed significant advances in therapeutic approaches for alloHSCT, including the use of alternative stem cell sources, less toxic conditioning regimens, and better supportive care, resulting in improved overall survival (OS) [1-5]. However, disease relapse remains the principal cause of treatment failure for these patients [6-9]. The risk of relapse varies from 20% to 60%, depending on the diagnosis and stage of the disease at the time of transplantation, and outcomes of salvage treatments are poor [10-12]. Median time to relapse after nonmyeloablative alloHSCT is 3 to 6 months and somewhat longer after myeloablative alloHSCT. Therefore, early maintenance therapy, directed at eliminating minimal residual disease and promoting a graft-versus-leukemia (GVL) effect, could be an effective method to improve outcomes after alloHSCT.

The concept of post-transplantation maintenance therapy with hypomethylating agents in AML and MDS has been

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initially studied by investigators at MD Anderson Cancer Center [13-15]. They showed that azacitidine (AZA) can be safely administered to heavily pretreated post-transplantation patients and may prolong event-free and OS. In addition, recent studies have shown that AZA, followed by donor lymphocyte infusion, is well tolerated when administered for early AML/MDS relapse after alloHSCT [16-18]. Decitabine (5-aza-2′-deoxycytidine) is a hypomethylating agent that irreversibly inhibits DNA methyltransferase I (DNMT-1), leading to genome-wide global DNA hypomethylation. Although AZA incorporates primarily into RNA and to the lesser extent DNA, decitabine is more selective, reducing only DNA methylation. In addition, decitabine is an approximately 5-fold more potent inhibitor of DNMT-1 than AZA is. Decitabine induces leukemic differentiation and re-expression of tumor-associated genes that had been epigenetically silenced [19]. At high doses, cells die from apoptosis triggered by DNA synthesis arrest, and at low doses, cells survive but change their gene expression profile to favor differentiation, reduced proliferation, and increased apoptosis. In addition, maximum effects of DNA hypomethylation have been observed at low doses and with less side-effects [20,21]. Decitabine has demonstrated activity in a variety of hematological malignances, including AML, MDS, and blast phase chronic myeloid leukemia [22-30]. It is generally well tolerated, with the primary toxicity being prolonged myelosuppression. Our group has demonstrated that decitabine enhances FOXP3 expression and can convert $CD4^+CD25^-FOXP3^-$ T cells into $CD4^+CD25^+FOXP3^+$ T regulatory cells (Tregs) [31,32]. Through their immunoregulatory properties Tregs are thought to play an important role in modulating graft-versus-host disease (GVHD) without sacrificing the beneficial GVL effect [33,34]. In addition, several other groups have demonstrated effects of DNA hypomethylating agents on T cell–mediated antitumor activity [35-39]. These include increasing tumor-specific CD8 T cell responses by upregulating tumor antigen expression on malignant cells and inducing expression of killer cell immunoglobulin–like receptor in T cells, thereby enhancing cytotoxic effector function of T cells against tumors. In human studies, patients noted to have a higher relative frequency of Tregs after HSCT had lower rate and severity of GVHD, lower rate of nonrelapse mortality (NRM), and equivalent relapse mortality [34].

Taken together, these studies provide a rationale for the administration of decitabine after alloHSCT for AML and MDS. We hypothesized that decitabine maintenance may provide direct antileukemic effect both to eradicate minimal residual disease and provide disease control by facilitating a GVL effect. In addition, decitabine may decrease the incidence of GVHD by enhancing the effect of Treg lymphocytes.

PATIENTS AND METHODS

This was a single-institution, open-label, prospective, dose-finding study of low-dose decitabine as a maintenance therapy after alloHSCT. The trial was approved by the institutional review board at the Washington University School of Medicine and informed consent was obtained in accordance with the Declaration of Helsinki. The trial was registered at www.clinicaltrials.gov (NCT00986804). Eisai Inc. provided decitabine for all enrolled patients.

Eligibility Criteria and Enrollment

Adults 18 years of age or older, with AML or MDS, who achieved a complete remission (CR) after alloHSCT were enrolled in the study between day +50 and +100 after alloHSCT. Exceptions were made for 3 patients who were enrolled shortly after day +100: for 2 patients, day +100 fell during the weekend/holiday, and for 1 patient, who was already consented, lived far away, and had transportation problems. *CR* was defined as $< 5\%$ blasts in the bone marrow with a count of at least 200 nucleated cells, no blasts with Auer rods, no extramedullary disease, absolute neutrophil count (ANC) $\geq 1500/\mu L$, platelet count $\geq 50{,}000/\mu L$, and no blasts in the peripheral blood. The higher threshold for ANC than that recommended by International Working Group (IWG), was chosen in anticipation of neutropenia secondary to decitabine and lower platelet threshold was allowed to facilitate enrollment. No platelet transfusion within 7 days of enrollment or growth factor support was allowed to meet those criteria. Other major eligibility criteria included Eastern Cooperative Oncology Group performance status ≤ 2, no grade 3 and 4 acute GVHD, no uncontrolled infection, creatinine $< 1.5 \times$ upper limit of normal (ULN), bilirubin $\leq 1.5 \times$ ULN, and hepatic enzymes $\leq 2.5 \times$ ULN. Both myeloablative and nonmyeloablative conditioning regimens were allowed, and both related and unrelated donors were permitted using either peripheral blood or bone marrow as a source of graft. Donors could be mismatched at a single antigen at HLA-A, -B, or -DR locus, plus a single antigen mismatch at HLA-C; 2-antigen mismatch at a single locus was not allowed. Acute GVHD prophylaxis was according to the treating physician.

Treatment Plan

Decitabine was administered as an intravenous infusion for 5 consecutive days every 6 weeks for up to 8 cycles. The study consisted of 5 escalating dose levels, only 1 of which was open for accrual at a given time. The first cohort of 4 patients started decitabine at 5 mg/m^2/day. In subsequent cohorts, the dose was escalated to 7.5, 10, and 15 mg/m^2/day according to the dose-limiting toxicity (DLT) experienced at the previous dose level. Decitabine dose could be de-escalated to 2.5 mg/m^2/day if a DLT were observed in the first cohort. There was an observation period of 42 days between enrolling each subsequent cohort.

The primary goal was to determine the *maximum tolerated dose* (MTD) of decitabine, defined as the maximum dose at which $\leq 25\%$ of patients experience DLT during the first cycle of treatment. *DLT* was defined as (1) ANC $< 500/\mu L$ and/or platelet count $< 30{,}000/\mu L$ sustained for 2 consecutive weeks without platelet transfusions, (2) inability to achieve ANC $\geq 1000/\mu L$ and platelet count $\geq 50{,}000/\mu L$ after a delay of the second cycle by a maximum 2 weeks, or (3) grade 3 and 4 nonhematological toxicities related to decitabine. Patients who met criteria for DLT started the second cycle at 1 level dose reduction. Patients with inadequate counts 6 weeks after a previous cycle had their next cycle delayed by maximum of 2 weeks. Each cohort could contain 4 or 8 evaluable patients until a MTD or a dose of 15 mg/m^2/day were reached. Patients with documented progressive disease were removed from the study.

Dose Adjustments

Dose adjustments were made as follows: If no DLT were observed in any of the 4 patients treated at the current dose-level, the current dose was deemed acceptable and the study proceeded with dose escalation. If a DLT were observed in 1 of 4 patients treated at current dose-level, then 4 additional patients were enrolled at same dose-level. If 1 of those 8 experienced a DLT, then the current dose was deemed acceptable and escalated; if 2 or more of 8 patients experienced DLTs, then the current dose was deemed over toxicity and the previous dose was considered MTD. If 2 or more of 4 patients experienced a DLT, the current dose was deemed over toxicity and the previous dose level was considered MTD.

Evaluation of Response

All patients completing the first cycle of decitabine were included in the safety and efficacy assessment. History, physical exam, complete blood count, and complete metabolic panel were performed at baseline and every 2 weeks thereafter. Bone marrow biopsy was performed at baseline, at cycle 3 day 1, and at cycle 8 day 42 (or at end of study for any reason). Acute and chronic GVHD evaluation were performed every 2 cycles or sooner, if clinically indicated. Chronic GVHD was diagnosed and graded according to the National Institutes of Health Criteria [40]. Determination of relapse was based on the peripheral blood, bone marrow biopsy, or evidence of new extramedullary disease. Patients were followed for survival and relapse for 5 years.

Toxicity Assessment

All patients receiving at least 1 dose of decitabine were included in the toxicity assessments. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. *Serious adverse event* was defined as any toxicity that met any of the following conditions: resulted in death, was life threatening, required hospitalization, or resulted in significant disability or incapacity. Toxicity assessment was performed at the beginning of each cycle.