

Gemtuzumab ozogamicin in combination with vorinostat and azacitidine in older patients with relapsed or refractory acute myeloid leukemia: a phase I/II study

Roland B. Walter,^{1,2,3} Bruno C. Medeiros,⁴ Kelda M. Gardner,¹ Kaysey F. Orlowski,¹ Leonel Gallegos,⁴ Bart L. Scott,^{1,5} Paul C. Hendrie,^{1,2} and Elihu H. Estey^{1,2}

¹Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; ²Department of Medicine, Division of Hematology, University of Washington, Seattle, WA; ³Department of Epidemiology, University of Washington, Seattle, WA; ⁴Stanford University, Stanford, CA; and ⁵Department of Medicine, Division of Medical Oncology, University of Washington, Seattle, WA, USA

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Correspondence: rwalter@fhcrc.org

DETAILED DESCRIPTION OF METHODS

Study population

Patients aged ≥ 50 years were eligible if they had a prior morphological diagnosis of AML other than acute promyelocytic leukemia according to the 2008 World Health Organization classification¹ and required either first salvage chemotherapy for primary refractory disease (as defined as persistent disease after 1 or 2 courses of conventional curative-intent chemotherapy) or relapsing disease with a duration of first CR < 12 months after at least one course of conventional curative-intent chemotherapy; patients with prior autologous or allogeneic hematopoietic cell transplantation (HCT) were eligible if relapse occurred 6-12 months post-transplant. Other inclusion criteria included: an Eastern Cooperative Oncology Group (ECOG) PS of 0-3; a white blood cell (WBC) count of $< 25,000/\mu\text{L}$; total bilirubin $\leq 1.5 \times$ Upper Limit of Normal (ULN) unless elevation was due to hepatic infiltration by AML, Gilbert's syndrome, or hemolysis; SGOT/SPGT $\leq 1.5 \times$ ULN unless elevation was due to hepatic infiltration by AML; serum creatinine $\leq 1.5 \times$ ULN; and left ventricular ejection fraction $\geq 40\%$. Exclusion criteria were: another malignancy, unless the patient was diagnosed at least 2 years earlier and had been disease-free for at least 6 months following completion of curative-intent therapy; relapsing/refractory blast crisis of chronic myeloid leukemia; prior therapy of AML with GO, vorinostat, or azacitine; central nervous system AML; and positive HIV test if CD4 count < 200 cell/ μL . Similarly excluded were pregnant or breastfeeding patients, as well as those with uncontrolled systemic infections. Cytogenetic risk-group assignment was done according to the modified United Kingdom Medical Research Council/National Cancer Research Institute (MRC/NCRI) criteria.² Treatment responses were defined according to standard criteria.^{3,4} The presence of MRD was assessed by multiparameter flow cytometry using the institution's routine methodology; any level of MRD was considered MRD^{pos}. The National Cancer Institute/Cancer Therapy Evaluation Program (NCI/CTEP) as well as the institutional review board of both participating institutions approved the protocol, and patients gave written informed consent in accordance with the Declaration of Helsinki. This trial was registered at ClinicalTrials.gov as NCT00895934.

Treatment plan

In this phase 1/2 study, the starting dose level (level 1) used azacitidine 75 mg/m²/day I.V. or S.C. on days 1-7, vorinostat 200 mg/day orally on days 1-9, and GO 3 mg/m² I.V. on day 8. At dose levels 2 and 3, the daily vorinostat dose was increased to 300 mg and 400 mg, respectively, while keeping the other drug doses unchanged. At the highest dose level (dose

level 4), GO 3 mg/m² was given on days 4 and 8 while keeping the other drug doses unchanged from level 3. If necessary, hydroxyurea was given to reduce the leukocyte count to <25,000/μL before beginning study therapy but was discontinued prior to initiation of treatment with vorinostat and azacitidine; this arbitrary cut-off was chosen because of the manufacturer's warning that patients with high peripheral blast counts may be at greater risk for pulmonary events and tumor lysis syndrome (leading to the recommendation to only administer GO if the peripheral white blood cell count is below 30,000/μL), and because of the theoretical concern that high CD33-antigen loads in the peripheral blood could consume GO and, consequently, limit CD33 saturation in the bone marrow.⁵ If there was clear evidence of persistent leukemia (>20% blasts in non-hypoplastic bone marrow) on day 15, the first cycle was repeated. In all other patients, a second cycle was begun if peripheral blood counts had recovered (blood count recovery was not required for patients with persistent leukemia) and all toxicities had resolved to ≤grade 2. Patients were removed from protocol if there was frank disease progression, as assessed in the peripheral blood (e.g. doubling of peripheral blast count compared to pretreatment and increase of blast count to >10,000/μL) and/or bone marrow (e.g. significant increase in total leukemia cell burden). Otherwise, patients came off study if a partial remission (PR; >50% decrease of bone marrow blast percentage) was not achieved by the end of cycle 3, or if a CR or CR with incomplete peripheral blood count recovery (CRi) was not achieved by the end of cycle 6.

Statistical considerations

To accomplish the primary objective of the study, a “3+3” dose escalation design for phase 1 and a Simon minimax two-stage design for phase 2 were used.⁶ Dose-limiting toxicities (DLTs) were defined as: 1) any grade 3 non-hematologic toxicity lasting >48 hours that results in >7 day delay of the subsequent treatment cycle, with the exception of febrile neutropenia or infection; 2) any grade ≥4 non-hematologic toxicity, with the exception of febrile neutropenia/infection or constitutional symptoms if recovery to grade ≤2 within 14 days; and 3) prolonged myelosuppression (platelet count <20,000/μL and/or absolute neutrophil count <500/μL at day 42 after treatment in patients without evidence of persistent leukemia). Cumulative toxicities were assessed after 2 cycles for determination of the toxicity endpoint of this study. Efficacy was determined as the best response achieved during study treatment. For this study, we considered a response rate of 0.17 as unacceptably low based on historical CR rate of 17% among 141 patients treated at MD Anderson Cancer Center with cytarabine-containing regimens for relapsed (CR1 <12 months) or primary refractory AML from 2000-2007 (13/81

patients aged <60 years, 11/60 patients aged ≥60 years; E.H. Estey, unpublished observation). We considered 0.34 (i.e. doubling of the rate of response) as an acceptably high response rate for the investigational regimen. We set at 0.1 both the probability of (incorrectly) accepting a regimen with a true response rate of 0.17 and of (incorrectly) rejecting a regimen with a true response rate of 0.34. Thus parameterized, the design called for treating 26 patients in the first stage, including the 6 patients treated at the recommended phase 2 dose from the phase 1 portion of the study. Accrual would stop if the response rate was $\leq 4/26$. If at least 5 responses were seen in the first 26 patients, 17 additional patients would be enrolled in the second stage, for a total of 43 patients treated at the recommended phase 2 dose, with a response rate of at least 11/43 needed to consider the regimen for further testing.

Follow-up

Follow-up data are current as of April 2013.

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