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A phase II trial of decitabine, bortezomib and pegylated liposomal doxorubicin for the treatment of relapsed or refractory AML

Brian A. Jonas [a,*], Laura A. Potter [b], Maria Galkin [c], Joseph M. Tuscano [a]

[a] Department of Internal Medicine, Division of Malignant Hematology, Cellular Therapy and Transplantation, University of California Davis School of Medicine, Sacramento, CA, USA
[b] University of California Davis School of Medicine, Sacramento, CA, USA
[c] Division of Hematology/Oncology, Tufts Medical Center, Boston, MA, USA

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1. Introduction

Relapsed/refractory (R/R) acute myeloid leukemia (AML) remains a challenge to cure. Proteasome inhibitors like bortezomib have inhibitory effects on nuclear factor kappa B (NF-κB) activity, which is thought to play a role in the development of anthracycline (AC) resistance [1]. Our previous clinical trial of bortezomib in combination with the AC pegylated liposomal doxorubicin (PLD) demonstrated safety and activity in patients with R/R AML, but the objective response rate (ORR) of 20% suggested that proteasome inhibition alone was insufficient to augment sensitivity to ACs [2]. Like proteasome inhibitors, the hypomethylating agents (HMAs) are also known to downregulate the NF-κB pathway, and prior studies have shown that the HMA decitabine has activity in R/R AML, both as monotherapy and in combination with bortezomib [3,4]. We hypothesized that synergistic suppression of NF-κB signaling by bortezomib and decitabine together could more effectively prevent development of AC resistance and yield a superior ORR. We thus conducted a phase II study of a triplet decitabine, bortezomib, and PLD (DBP) regimen, with a safety lead-in cohort, in patients with R/R AML (NCT01736943).

2. Materials and methods

The protocol was approved by the UC Davis Institutional Review Board, and all patients provided informed consent. Adult patients with AML aged 18–90 and unlikely to respond to conventional therapy, including both those with R/R disease after 1–4 prior induction regimens and those with newly diagnosed AML who were unfit for or declined standard therapy, were eligible. Patients with acute promyelocytic leukemia (M3 subtype), baseline grade 2+ peripheral neuropathy, myocardial infarction within 6 months prior to enrollment, New York Heart Association Class III or IV heart failure, uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia or active conduction system abnormalities, human immunodeficiency virus, active or uncontrolled central nervous system leukemia, baseline serum bilirubin >1.5 mg/dL, baseline aspartate transaminase or alanine transaminase >3 times the institutional upper limits of normal, or who had received radiation therapy within 3 weeks or prior anti-AML chemotherapy within 2 weeks or 5 half-lives were excluded.

The original protocol called for up to four 28-day cycles of induction with intravenous decitabine 20 mg/m^2 on days 1–10, subcutaneous bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, and intravenous PLD 40 mg/m^2 on day 4. Dose-limiting toxicity (DLT) of grade 3 peripheral neuropathy in the first 2 patients led to a revised schedule of bortezomib on days 5, 8, 12, and 15 and PLD on day 12 to eliminate simultaneous DBP dosing. Patients achieving a bone marrow blast count <5% after any course of induction proceeded to the continuation regimen: 28-day cycles of decitabine on days 1–5, bortezomib on days 1 and 8, and PLD on day 12. Treatment continued until progression, intolerance, bone marrow transplant (BMT), study withdrawal, or administration of 12 cycles. Patients reaching lifetime maximum AC exposure could remain

* Corresponding author at: UC Davis Comprehensive Cancer Center, 4501 X St, Suite #3016, Sacramento, CA 95817.
E-mail address: bajonas@ucdavis.edu (B.A. Jonas).

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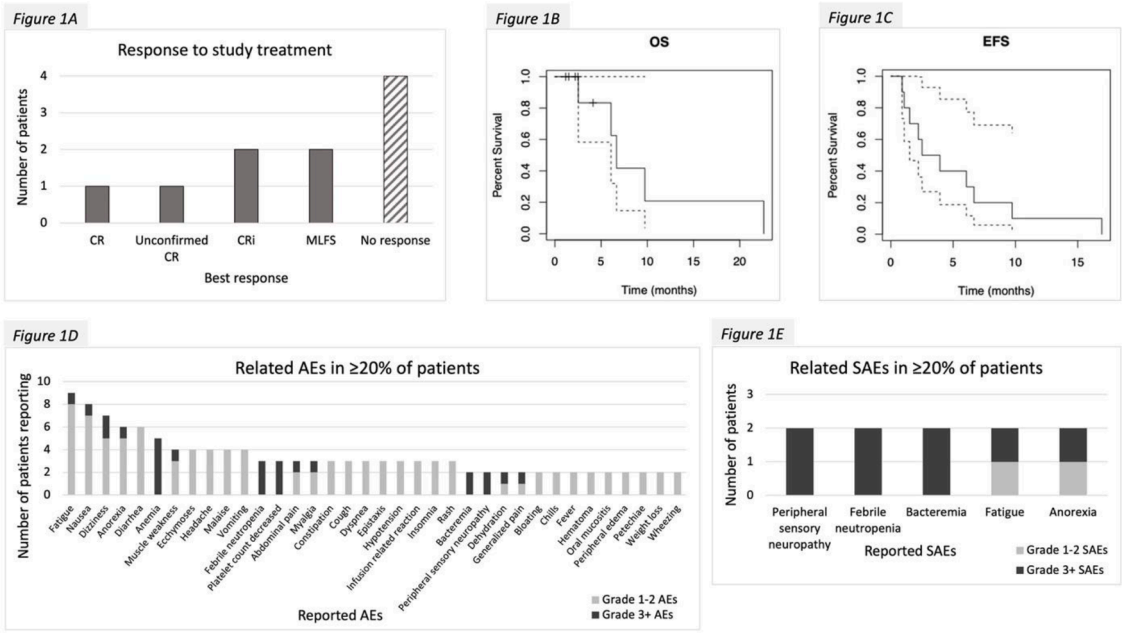

Fig. 1. ***A*** *(top left).* Response to study treatment. CR, complete remission; CRi, complete remission with incomplete hematological recovery; MLFS, morphological leukemia-free state. ***B*** *(top center).* Overall Survival Kaplan-Meier Curve. OS, overall survival. ***C*** *(top right).* Event-Free Survival Kaplan-Meier Curve. EFS, event-free survival. ***D*** *(bottom left).* Related AEs occurring in ≥20% of patients. Aes, adverse events. ***E*** *(bottom right).* Related SAEs occurring in ≥20% of patients. SAEs, serious adverse events.

on trial with PLD removed from their regimen.

The primary endpoint was objective response rate (ORR), defined as complete remission (CR) + CR with incomplete hematological recovery (CRi) + partial remission. Response was based on International Working Group criteria and determined by blood count values between cycles [5]. Secondary endpoints of overall and event-free survival (OS, EFS) were estimated by Kaplan-Meier method, with OS defined as time from treatment initiation to death and EFS defined as time from treatment initiation to first instance of relapse, refractory disease, or death. Survivors were censored at their date of last follow-up. Both primary and secondary endpoint analyses used the intent-to-treat dataset, defined as all eligible patients enrolled in the study. We estimated the ORR in R/R AML patients treated with a 10-day decitabine regimen to be approximately 16%. Assuming a one-sided type I error rate of 5% and 80% power, a 30% increase in ORR with the addition of bortezomib and PLD to 46% would conclude that DBP elicits an ORR significantly greater than decitabine alone. Additionally, we posited that ≥5 responses out of a planned 14 total patients (35.7%) would deem this regimen sufficiently active to warrant further study in larger, more definitive trials.

Toxicity was monitored per Common Terminology Criteria for Adverse Events (AEs) v4.03. For the purposes of safety analysis, toxicity data were summarized by AE incidence at maximum grade, stratified by severity and relation to study treatment. All statistical analyses were performed using *R* (R Foundational for Statistical Computing, Vienna, Austria).

3. Results

Ten patients were enrolled from May 2016 to February 2018, after which the funding source closed the protocol. Baseline characteristics are presented in Supplemental Table 1. Median age was 57 years [range 27–69]. Patients were 50% female, 60% White, 10% African American/Black, 30% other/mixed race, and 40% Hispanic/Latino, and median baseline ECOG score was 1 [range 0–1]. All ten enrolled patients had R/R disease with a median of 2 [range 1–3] lines of prior therapy. Sixty percent had *de novo* and 40% had secondary disease. By WHO subtype, 30% had AML with myelodysplasia-related changes, 20% AML with mutated *NPM1*, 10% AML with inv(3)(q21.3q26.2);*GATA2, MECOM*, 10% therapy-related myeloid neoplasms, and 30% AML, not otherwise specified. European LeukemiaNet 2022 risk was favorable in 20%, intermediate in 60%, and adverse in 20% [6].

Median number of cycles completed was 2 [1–7] with a median time on study of 100.5 days [35–678]. As shown in Fig. 1A, one patient achieved CR and 2 achieved CRi for an ORR of 30%. One other patient likely had a CR with count recovery and 4% blasts by both flow cytometry and immunohistochemistry but had a suboptimal aspirate differential; including this unconfirmed CR, ORR was 40%. An additional 2 (20%) achieved morphological leukemia-free state (MLFS) for a total of 6 patients (60%) with any anti-leukemia response (CR + CRi + PR + MLFS). Of the 6 responders, 2 achieved best response after cycle 1, 2 after cycle 2, 1 after cycle 3, and 1 after cycle 4. Relapse after any anti-leukemia response occurred in 2 of 5 (40%) while on study, at 425 days after CRi and 83 days after MLFS. All 3 patients with prior HMA exposure were non-responders.

All patients discontinued treatment. Reasons included BMT (40%), AE (30%), progression (20%) and insurance loss (10%). Half planned to bridge to BMT as next-line therapy following study treatment. When taken off study, 50% were alive while 20% had died from AML complications, 20% from graft-versus-host-disease post-BMT, and 10% after relapse post-BMT. Median OS was 6.67 months (95% confidence interval [CI] 6.07 to not reached [NR]), with a range of 2.53 to 22.60 months (see Fig. 1B). Median EFS was 3.22 months (95% CI 1.50 to NR), with a range of 0.90 to 16.93 months (see Fig. 1C).

Following grade 3 peripheral neuropathy in the first 2 patients, no DLTs occurred on the modified regimen. Grade 3+ AEs and serious AEs (SAEs) of any grade occurred in 90% and 80% of patients, respectively. Of the 22 related grade 3+ AEs, anemia and decreased platelet count were seen in 50% and dizziness in 20%. Of the 22 related SAEs, anorexia, fatigue, peripheral neuropathy, febrile neutropenia, and bacteremia were most common, each occurring in 20%. All related AEs and SAEs occurring in ≥20% of patients are presented in Figs. 1D-E. For a summary of all AEs and SAEs occurring in ≥20% of patients, regardless of attribution to study treatment, see Supplemental Figures 1–2.

4. Discussion

Overall, the observed AEs in this study were in line with expectations for the patient population and known side effects of the study drugs per previous studies. Hematological toxicities, including thrombocytopenia, anemia, and both febrile and nonfebrile neutropenia, are common to both the natural history of AML and its pharmacotherapeutics, including all three drugs used in this regimen. Many AEs observed in our trial, such as fatigue, myalgia, muscle weakness, and peripheral neuropathy, are known side effects of bortezomib; similarly, PLD commonly causes gastrointestinal upset. The DLT of grade 3 peripheral neuropathy seen in the first two patients on the simultaneous DBP dosing schedule was suggestive of a synergistic toxic effect; however, modification to a staggered dosing schedule was able to prevent this toxicity and improve treatment tolerability.

5. Conclusions

In conclusion, the DBP triplet demonstrated preliminary anti-AML activity and a tolerable safety profile in patients with R/R AML. Staggered dosing was better tolerated than simultaneous DBP, and toxicities in general were consistent with the patient population and agents tested. Our results suggest that DBP may serve as an effective bridge to BMT for some patients. Including the unconfirmed CR, our ORR of 40% is below the 46% threshold for concluding that DBP elicits a superior response to decitabine alone but nevertheless exceeds the 35.7% cutoff justifying further study of this regimen in larger trials. As such, this study supports further evaluation of DBP, or related combinations, in R/R AML.

CRediT authorship contribution statement

Brian A. Jonas: Conceptualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Laura A. Potter:** Formal analysis, Writing – original draft, Writing – review & editing. **Maria Galkin:** Formal analysis, Writing – original draft, Writing – review & editing. **Joseph M. Tuscano:** Conceptualization, Investigation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

B.A.J.: Consultant/advisor for AbbVie, BMS, Daiichi Sankyo, Genentech, Gilead, GlycoMimetics, Jazz, Kymera, Pfizer, Rigel, Servier, and Takeda; protocol steering committee for GlycoMimetics; data monitoring committee for Gilead; travel reimbursement/support from AbbVie and Rigel; institutional research funding from AbbVie, Amgen, Aptose, AROG, BMS, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche, Forma, Forty-Seven, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Incyte, Jazz, Loxo Oncology, Pfizer, Pharmacyclics, Sigma Tau, and Treadwell.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lrr.2023.100374.

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