Metronomic low-dose regimen of decitabine and venetoclax is safe and reduces monocyte burden in chronic myelomonocytic leukemia

Chronic myelomonocytic leukemia (CMML) is a myeloid neoplasm with features both of myelodysplastic syndromes (MDS) and myeloproliferative neoplasms (MPN), that has a high propensity to transform into acute myeloid leukemia (AML). Allogeneic stem cell transplant (alloSCT) is the only available cure but is reserved for younger fit patients. Hypomethylating agents (HMA) are currently the only Food and Drug Administration (FDA)-approved therapies for CMML based on trials that predominantly enrolled patients with MDS and only a fraction with CMML. In fact, the only phase III trial that exclusively enrolled CMML patients and compared HMA to hydroxyurea did not show an event-free or overall survival (OS) benefit for HMA over hydroxyurea.[1,2] This was despite the higher response rate in the HMA arm, as this was offset by increased toxicity related to infections from myelosuppression. Optimizing the dosing schedule of HMA therapy in CMML may overcome toxicity, thereby enhancing the efficacy and survival benefits.

Venetoclax (Ven) is a BCL-2 inhibitor that, when combined with HMA, is the current standard of care for elderly or frail patients with AML[3] unfit for "intensive chemotherapy." Similar to AML, the addition of Ven to HMA in MDS[4] has been challenging due to myelosuppression with the current practice of prolonged and continuous Ven exposure. In two previous studies decitabine, administered by a minimum biologically effective dose (MBD) to produce HMA effects ("low-dose decitabine") administered once a week ("metronomic") combined with Ven, also given weekly, was shown to be effective and well tolerated in elderly and frail patients with AML and MDS, including heavily pre-treated patients with poor bone marrow (BM) reserves.[5,6] The addition of Ven to HMA therapy has been tried in CMML but is limited to retrospective experiences. Using continuous Ven, per the current FDA label in AML, has resulted in 100% of patients having grade 3-4 cytopenic adverse events.[7] In addition, outcomes do not appear improved over single agent HMA despite decreases in dosing schedules to mitigate toxicities.[8] Here, in an effort to rationalize the HMA/Ven combination towards decreasing toxicities and risks while maintaining potential efficacy benefits, we report the results of a retrospective cohort study of newly diagnosed CMML patients treated with metronomic weekly low-dose decitabine and Ven at Montefiore Einstein Comprehensive Cancer Center.

Eligible patients had histologically confirmed CMML by World Health Organization (WHO) criteria. Patients received decitabine 0.2 mg/kg subcutaneous injection and Ven 400 mg by mouth on days 1, 8, 15 and 22 of a 28-day cycle. Full methods have previously been reported.[6] The study was designed according to Good Clinical Practice Guidelines and the Declaration of Helsinki.

The primary objective was to assess CMML response criteria, defined by the 2015 MDS/MPN International Working Group.[9] Secondarily, we assessed changes in cytopenias over time. Mortality and length of therapy are also re-

Table 1. Baseline characteristics.

Baseline characteristics	Values
Age, years, median (range)	73 (65-81)
Male, N (%)	7 (88)
WBC x10^9/L, median	14
ANC x10^9/L, median (range)	0.66 (0.5-20)
Monocytes x10^9/L, median	6.15
Hb, g/dL, median (range)	11.2 (6.9-12.8)
Hb <10 g/dL, N (%)	4 (50)
Platelets x10^9/L, median (range)	80 (36-301)
Bone marrow blasts >5%, N (%)	3 (38)
Transfusion dependence, N (%)	4 (50)
CPSS-Mol low risk, N (%)	3 (38)
CPSS-Mol intermediate risk, N (%)	4 (50)
CPSS-Mol high risk, N (%)	1 (12)
Patient	**Indication for treatment**
1	Thrombocytopenia transfusion-dependent
2	Anemia, thrombocytopenia
3	Rising *KRAS* mutation
4	Anemia, moderate neutropenia, intermediate CPSS
5	Moderate-high IPSS intermediate CPSS
6	Severe neutropenia, ANC 0.5x10^9/L
7	High IPSS, intermediate CPSS
8	Very high IPSS, high CPSS

WBC: white blood cell count; ANC: absolute neutrophil count; Hb: hemoglobin; CPSS-Mol: clinical/molecular chronic myelomonocytic leukemia-specific prognostic scoring system; IPSS: International Prognostic Scoring System.

ported. Hospitalizations are reported to assess safety and adverse events. Statistical analysis was performed using a repeated-measures ANOVA to compare values of monocytes. The significance value was preset at a *P* valueof 0.05.

Between May 2020 and March 2025, eight patients were diagnosed with CMML and began treatment with metronomic decitabine and Ven. Seven were male. Median age at diagnosis was 73 years. At diagnosis, median white blood cell count (WBC) was 14x10^9/L (range, 5-57x10^9/L), absolute neutrophil count (ANC) was 0.66x10^9/L (range, 0.66-2.23x10^9/L), monocytes were 6.15x10^9/L, 1.8-15.1x109/L, hemoglobin (Hb) was 11.2 g/dL (range, 8.2-14.9 g/dL), and platelets were 80x10^9/L (range, 5-487x10^9/L). Half of the patient were transfusion dependent at baseline. By International Prognostic Scoring System-Molecular criteria, two patients were low-risk, four were moderate-risk, and two were high-risk and by CMML-specific prognostic scoring system-Molecular, three patients were low-risk, four were moderate-risk, and one was high-risk. All eight patients were CMML-1 per WHO 2022 criteria, five were proliferative type and three were dysplastic type. The most common mutations were *SRSF2, TET2* and *NRAS* (4 patients each), followed by *CBL* (3 patients). *ASXL1* was seen in 1 patient. Baseline characteristics are displayed in Table 1.

After 3 months of treatment, median WBC decreased to 5.6x10^9/L, ANC to 2.63x10^9/L and monocytes to 0.625x10^9/L, while Hb was 11.4 g/dL and platelets were 113x10^9/L. After

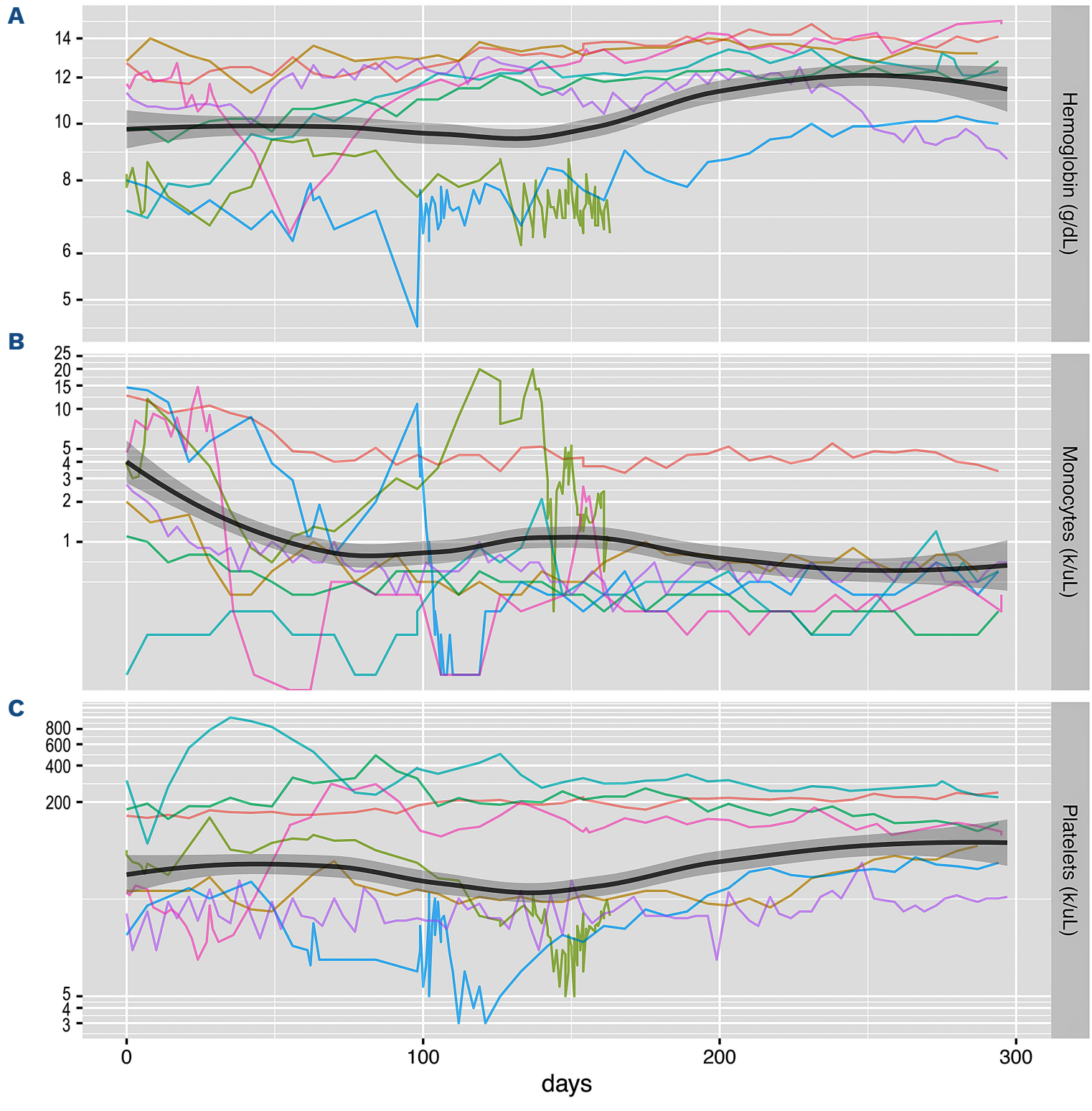

Figure 1. Changes in cytopenias. (A) Monocyte count, (B) hemoglobin, (C) platelet count. (B) Monocyte count significantly decreases (*P*=0.00158) over time, while (A) hemoglobin and (C) platelet count do not decrease and in fact slightly increase, although not significantly. Individual patients 1-8 represented by different colors. Black line indicates the median count.

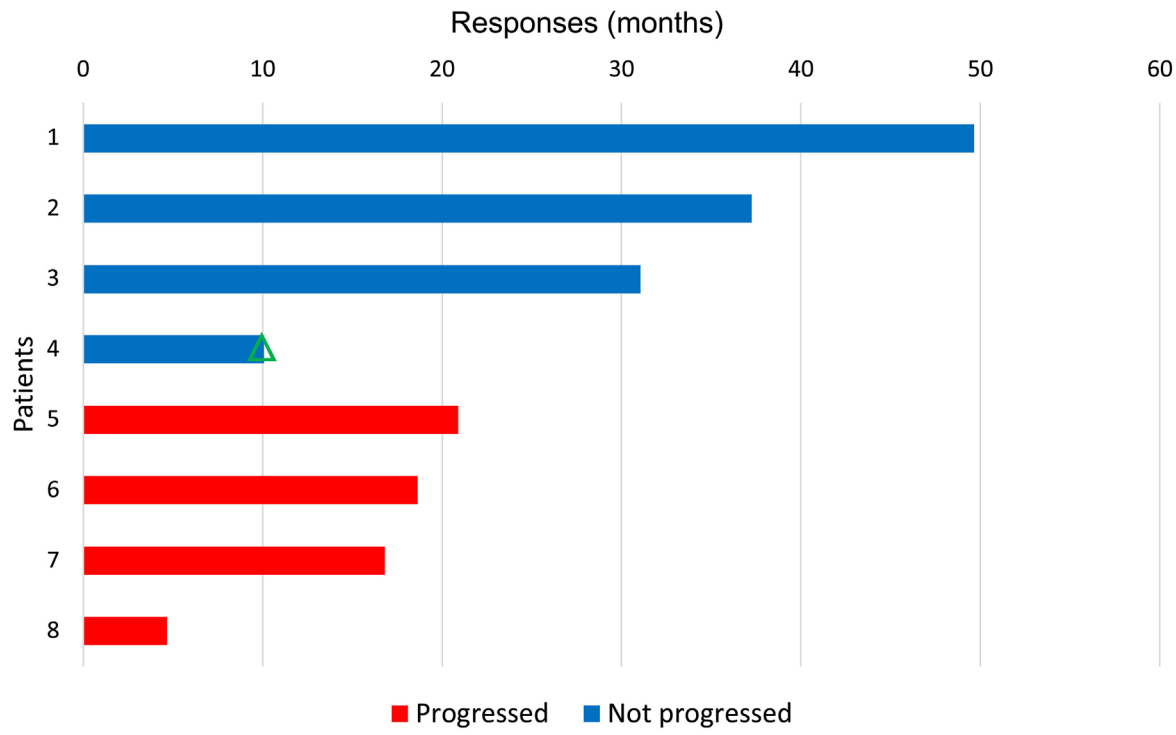

Figure 2. Individual patient responses. Patient went onto allogeneic stem cell transplant.

6 months of treatment, median WBC continued to decrease to 0.475x10^9/L, ANC 2.85x10^9/L and monocytes to 0.5x10^9/L, while Hb increased to 12.4 g/dL and platelets to 141x10^9/L. After 12 months of treatment, median WBC was 6.15x10^9/L, ANC 4.0x10^9/L, and monocytes 0.7x10^9/L, while Hb was 11.9 g/dL and platelets were 75x10^9/L. Monocytes decreased significantly over time (P=0.00158). Changes in cytopenias are shown in Figure 1. Of the four patients transfusion-dependent at diagnosis, three (75%) became transfusion independent. According to the 2015 MDS/MPN International Working Group criteria, five patients achieved a complete response, one achieved a partial response, and two had clinical benefit at 3 months. At 6 months, three patients remained in a complete response and one had progression of disease. At 12 months, two patients remained in a complete response. For the three patients with BM blasts >5% at baseline, only two had BM biopsies to assess their response and both had BM blasts <5% at 3 months. One continued with BM blasts <5% for 12 months and the other did not have an evaluable BM biopsy after 3 months. Individual responses are shown in Figure 2.

Three patients died during the study: two from progression to AML and the third from cardiac tamponade possibly related to CMML (thought to be progressing but died before BM assessment). All three patients who died had a BM blast count >5% at the time of diagnosis. Of the patients who died, the median length of therapy was 16.8 months. For all patients, the median length of therapy was 18.9 months, with three of the five alive patients still on therapy at time of writing (1 lost to follow-up and 1 received successful alloSCT). Median event-free survival was 20.9 months. Three patients required hospitalization during the first 6 months: one for progression to AML, one for symptomatic anemia, and one for syncope due to hypotension/dehydration. Throughout the entire treatment period, there were seven hospitalizations among three (38%) patients and there were no hospitalizations for febrile neutropenia. Five (63%) patients experienced ≥3 neutropenia (ANC <1.0x10^9/L). Three patients (38%) experienced grade 4 neutropenia (ANC <0.5x10^9/L); one for 2 days, one for 7 days, and one for 1 month. Grade ≥3 thrombocytopenia occurred in five (63%) patients.

Despite recent improvements in novel therapies for MDS and AML, there has been limited progress in CMML. The addition of Ven to HMA therapy has not to date, been shown to improve OS in CMML. This may be a result of toxicity with single-agent HMA, leaving no room for toxicity of an additional agent. To address this an expert panel recently recommended that it will be prudent to identify drug dosages that maximize not only efficacy but also safety and tolerability.[10] In other words finding an “optimal dosage” as opposed to the “maximum tolerated dose” using the totality of pharmacokinetic, pharmacodynamic, safety, and exposure-response data.[10] Currently approved doses of HMA in CMML, despite showing efficacy, have been limited by myelotoxicity, abrogating any long-term benefit without showing an improvement in OS. An additional challenge is that the toxicity with currently approved HMA backbones has hampered the ability to safely add a doublet such as Ven which also causes marrow suppression and cytopenias. Here we show a proof of concept that metronomic once weekly low-dose decitabine with Ven is a safe, non-myelosuppressive treatment for CMML, with a promising signal of efficacy. Most importantly we show that low-dose decitabine with Ven significantly lowers monocytes count (on-target effect) with minimal toxicity is other cell lines by preserving functioning hematopoietic cells. Responses were seen in all patients, including 5 patients achieving a complete response. The main reason for the others not achieving a complete response was

the high threshold of 100x10^9/L for a platelet response. The patients who achieved a partial response and had clinical benefit, all had a drop in monocyte count which demonstrates a benefit of this regimen.

We also show that patients remain on therapy for a significant time. The median time on treatment was 26.0 months, including 16.8 months for those who progressed. While much of this may be limited to patients with low-risk and intermediate-risk disease, the long participation for patients who eventually progressed shows significant value in low-dose as a therapeutic option. Additionally, determining when to initiate treatment *versus* adopting a "watch and wait" approach is often challenging in CMML, due to variability in clinical practice regarding the optimal timing to start therapy. Therefore, the availability of well-tolerated treatments may lower the threshold for initiating therapy.

Limitations of our study include: small sample size and retrospective single center experience with a lack of a comparative cohort in a heterogeneous disease. Future prospective trials will be needed to fully assess the safety and efficacy of low-dose decitabine with Ven in CMML. Expanding to include quality of life metrics, like fatigue scores which have been validated in non-malignant hematologic diseases such as immune thrombocytopenia[11] and suggested in CMML and MDS,[12] would help assess if the decrease in monocytes correlates to a change in quality of life.

Authors

Bradley Rockwell,[1] Mendel Goldfinger,[1] Ioannis Mantzaris,[1] Aditi Shastri,[1] Yogen Saunthararajah,[2] Kira Gritsman,[1] R. Alejandro Sica,[1] Noah Kornblum,[1] Nishi Shah,[1] David Levitz,[1] Lauren C. Shapiro,[1] Ridhi Gupta,[1] Anne Munoz,[1] Aradhika Dhawan,[1] Karen Fehn,[1] Monica Comas,[1] Jhannine Verceles,[1] Dennis L. Cooper,[1] Marina Konopleva,[1] Eric J. Feldman[1] and Amit Verma[1]

[1]Department of Oncology, Montefiore Einstein Comprehensive Cancer Center, Albert Einstein College of Medicine, Bronx, NY and [2]Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Correspondence:
M. GOLDFINGER - mgoldfin@montefiore.org

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Contributions

BR designed and performed research and collected, analyzed, and interpreted data and wrote and revised the manuscript. MG and AV designed and performed research, analyzed and interpreted data, and reviewed, edited, and revised the manuscript. IM, AS, YS, KG, RAS, NK, DL, RG, MC, NS, LCS, DLC, EJF and MK performed research, analyzed and interpreted data, and reviewed and edited the manuscript. AM, AD, KF, and JV performed research and collected, analyzed, and interpreted data.

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Data-sharing statement

For original data of this study please contact the corresponding author. De-identified individual participant data will be made available for academic purposes following publication, subject to institutional approval.

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