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Letter

Integrating multi-omics methods for personalized treatment of refractory chronic myelomonocytic leukemia with *NRAS* and *TET2* mutations☆

Chuandong Hou [a,b,1], Bo Yang [a,1], Yue Wang [c,1], Lili Cai [d], Ran Qin [a], Bo Guo [a], Jie Geng [e], XueChun Lu [a,*]

[a] Department of Hematology, The Second Medical Center, Chinese PLA General Hospital, Beijing 100853, China
[b] Medical School of Chinese PLA, Beijing 100853, China
[c] National Institutes for Food and Drug Control, Beijing 102629, China
[d] Department of Laboratory Medicine, The Second Medical Center, Chinese PLA General Hospital, Beijing 100853, China
[e] School of Basic Medical Sciences, Shanxi Medical University, Taiyuan, Shanxi 030002, China

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Chronic myelomonocytic leukemia (CMML), a rare and malignant hematologic disorder, is classified as a myelodysplastic/myeloproliferative neoplasm (MDS/MPN).[1] It poses a significant risk of progression to acute myeloid leukemia and is generally associated with a poor prognosis.[2] CMML predominantly affects older adults, and treatment often involves demethylation therapy tailored to the patient's age and overall health.[3] However, the complete remission rate for patients with CMML undergoing demethylation therapy is <20% and is frequently accompanied with severe side effects.[1] Here, we discuss the case of an 84-year-old male diagnosed with CMML 6 years earlier, who experienced significant bone marrow suppression following demethylation therapy. By integrating multiomics data with bioinformatics, we developed and applied a novel approach of trimetinib monotherapy. This treatment resulted in notable improvements in hematopoietic function and overall quality of life, offering a promising strategy for managing CMML.

In April 2017, routine health checkups revealed that the patient had a low platelet (PLT) count. Subsequent bone marrow tests led to a diagnosis of immune thrombocytopenia (ITP). The patient was treated with glucocorticoids and a thrombopoietin receptor agonist, but the response was unsatisfactory. One year later, the patient was re-hospitalized due to prolonged skin and oral bleeding. Routine blood tests at that time showed the following results: white blood cell (WBC) of 9.50 × 10^9/L, hemoglobin (Hb) of 110 g/L, PLT of 10 × 10^9/L, and a monocyte percentage of 17% (absolute value 1.615 × 10^9/L) [Figure 1A]. Based on the persistently elevated peripheral blood monocyte count and other laboratory findings, the patient was diagnosed with CMML. Given the patient's advanced age and poor overall health, a demethylation treatment strategy was initiated as the first-line approach. However, after three cycles of decitabine, there was no significant improvement in the patient's peripheral blood PLT levels [Figure 1A]. Subsequently, long-term treatment with 25 mg of eltrombopag daily was started, accompanied by weekly PLT transfusions to sustain therapy. In December 2020, the patient's condition deteriorated, with significant abdominal distension and multiple swellings across the body. Computed tomography (CT) imaging revealed splenomegaly and enlarged axillary lymph nodes. Positron emission tomography (PET)/CT results showed widespread lymph node enlargement (maximum standardized uptake value [SUVmax] 4.7) and a marked increase in spleen size compared to scans from June of the same year [Figure 1B]. A left axillary lymph node excisional biopsy confirmed extramedullary infiltration consistent with CMML. As the patient had shown resistance to decitabine during previous treatment, two cycles of azacitidine were administered (regimen outlined in Figure 1A). However, bone marrow assessments indicated disease progression. A combined treatment regimen of decitabine and azacitidine was then implemented. After two cycles of this combination therapy, the patient's splenic length decreased from 17.7 cm to 14.9 cm [Figure 1A]. Despite a reduction in tumor cell burden, bone marrow tests revealed extreme hypoplasia, indicating severe bone marrow suppression. At this stage, the patient's PLT count dropped to 2 × 10^9/L, significantly increasing the risk of bleeding. Additionally, the patient's creatinine level rose to 143 μmol/L, indicating impaired kidney function. The patient's health status and laboratory findings confirmed that the demethylation therapy had failed. With no viable alternatives, we

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* Corresponding author: Department of Hematology, The Second Medical Center, Chinese PLA General Hospital, Beijing 100853, China.
E-mail address: luxuechun@301hospital.com.cn (X. Lu).

[1] Chuandong Hou, Bo Yang and Yue Wang contributed equally to this work.

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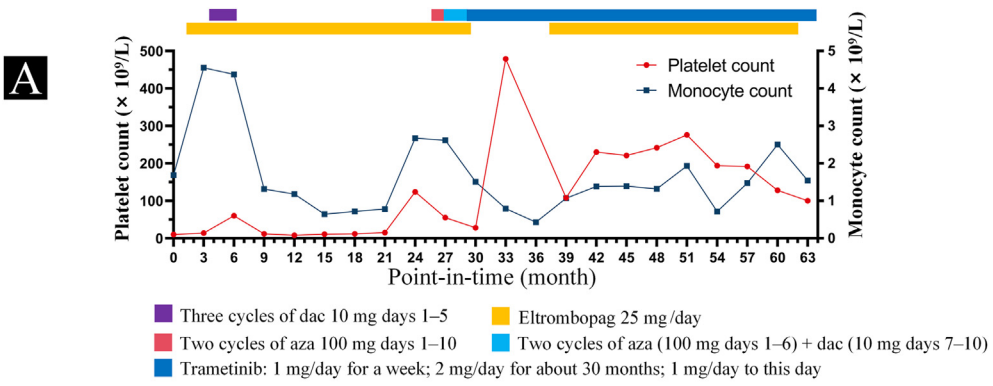

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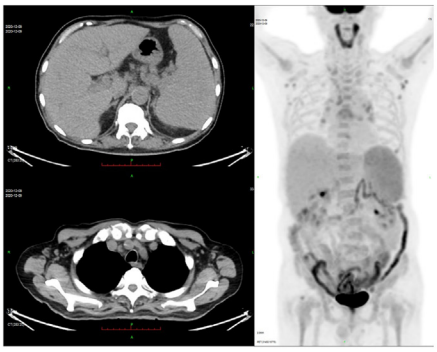
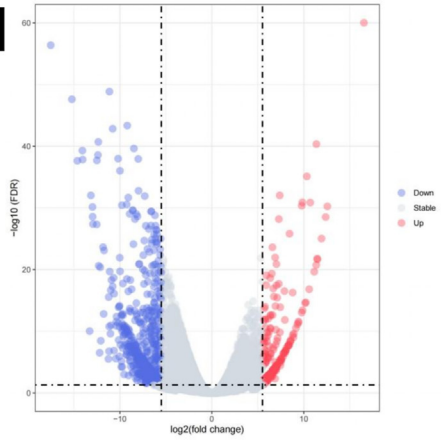


C

Name	Drug response	DScore
Trametinib	Sensivity	0.920
Sorafenib	Sensivity	0.917
Regorafenib	Sensivity	0.912
Copanlisib	Sensivity	0.904
Arsenic trioxide	Sensivity	0.902
Bosutinib	Sensivity	0.901
Cetuximab	Sensivity	0.815
Panitumumab	Sensivity	0.815
Ribociclib	Sensivity	0.814
Dabrafenib	Sensivity	0.813

D



E

Name	Drug response	Correlation
Decitabine	Sensivity	−0.50
Trametinib	Sensivity	−0.38
Valdecoxib	Sensivity	−0.38
Vinpocetine	Sensivity	−0.38
Tizanidine	Sensivity	−0.38
Treprostinil	Sensivity	−0.38
Chloroquine	Sensivity	−0.38
Clonidine	Sensivity	−0.38
Darinaparsin	Sensivity	−0.38
Sirolimus	Sensivity	−0.38

Figure 1. Treatment timeline, imaging examination, and drug prediction results. (A) Treatment plan and corresponding peripheral blood platelet and monocyte counts (dac represents decitabine; aza represents azacitidine). (B) CT images of the lower left corner show splenomegaly; CT results of the lower left corner show enlarged axillary lymph nodes. The right image shows the PET/CT results. (C) PanDrugs database predicted drug list (top 10). (D) The patient's transcriptome differential expression analysis. (E) EpiMed database predicted drug list (top 10). aza: Azacitidine; CT: Computed tomography; dac: Decitabine; FDR: False discovery rate; PET: Positron emission tomography.

utilized multi-omics data and bioinformatics analyses to identify new treatment options for the patient.

We first performed gene mutation analysis of the patient's bone marrow and identified two mutations: *NRAS* (p.G12D, 44.01%) and *TET2* (p.Q740X, 44.28%). Using the PanDrugs database,[4] we predicted targeted therapies for these mutations, as illustrated in Figure 1C. To further refine the drug selection, we conducted whole-transcriptome sequencing of the patient's peripheral blood. Differential messenger RNA (mRNA) expression analysis revealed 282 upregulated and 772 downregulated differentially expressed genes (DEGs), as shown in Figure 1D. The top five upregulated genes were *IGKC*, *PDXDC2P*, *RPSAP58*, *PYURF*, and *NBPF20*, while the top five downregulated genes were *EEF1G*, *PTPRCAP*, *WDR83OS*, *SAP25*, and *XIST*.

Next, we utilized our team's proprietary epigenetic precision medicine prediction database (EpiMed)[5] to identify drugs capable of negatively regulating the patient's DEGs. The drug prediction results from EpiMed are presented in Figure 1E. By intersecting the drug prediction lists from PanDrugs and EpiMed, we identified trametinib as a potential therapeutic candidate.

The patient was started on oral trametinib at a dose of 1 mg once daily. After 1 week without adverse events, the trametinib dose was increased to 2 mg/day, in combination with eltrombopag at 25 mg daily. Two weeks later, the patient's creatinine level gradually decreased to 111 μmol/L, bleeding symptoms resolved, and the need for PLT transfusion therapy was eliminated. After 30 months of treatment, the patient demonstrated significant improvement, with PLT counts rising to 280 × 10⁹/L and spleen size reducing to 12.5 cm × 5.3 cm. Ultimately, eltrombopag treatment was discontinued, and the trametinib dose was reduced to 1 mg/day, continuing with monotherapy to this day. The patient has now survived for 7 years without disease progression, with a significantly improved quality of life.

Our patient, who initially presented with thrombocytopenia, was diagnosed with ITP and underwent appropriate treatment; however, the response was unsatisfactory. Studies indicate that approximately 20% of

patients with MDS or MDS/MPN are misdiagnosed as having ITP.[6] This underscores the importance of conducting retrospective analyses to reassess the diagnoses of patients with ITP who fail to respond to conventional treatments. Following the diagnosis of CMML, the patient underwent seven cycles of demethylation therapy, which ultimately proved ineffective. Genetic mutation testing revealed mutations in *NRAS* and *TET2*. Research has shown that mutations in Ras signaling pathway-related genes (such as *NRAS* and *KRAS*) can activate mitogen-activated extracellular signal-regulated kinase (MEK) and its downstream pathways, leading to excessive tumor cell proliferation and low PLT levels.[7,8] Trametinib, a specific MEK inhibitor, is commonly used to treat unresectable or metastatic melanomas harboring *BRAFV600E* and *V600K* mutations.[9] However, a multicenter clinical trial (NCT00920140) demonstrated that oral trametinib monotherapy also has therapeutic effects on refractory or relapsed myeloid malignancies with Ras-related gene mutations. Trametinib has been shown to suppress tumor cell proliferation and increase PLT levels in affected patients.[10] Furthermore, Arnold Kloos et al. found that a combination of azacitidine and trametinib additively inhibits extracellular signal-regulated kinase phosphorylation, thereby depleting signaling from mutated *NRAS*.[11] However, the presence of a *TET2* mutation in our patient reduced sensitivity to demethylation therapies.[12] Given the patient's prior failure with demethylation therapy and their poor overall health, trametinib monotherapy was determined to be the most suitable treatment option.[13]

In summary, the study successfully identified trametinib as an effective treatment for CMML with *NRAS* and *TET2* mutations through the integration of multi-omics data and bioinformatics methods. This case serves as a representative example of the complex clinical challenges our team has addressed. Future clinical trials of trametinib should include a larger cohort of patients with refractory CMML to further investigate its mechanisms of efficacy.

Authors contribution

Chuandong Hou, Bo Yang and Yue Wang: study design, data collection, analysis, and interpretation; Lili Cai, Bo Guo, and Ran Qin: preparation of pathological materials and clinical data; Jie Geng: bioinformatics analysis and drug prediction; Xuechun Lu: writing – review and editing, funding acquisition. All the authors have read and approved the final version of the manuscript.

Ethics statement

This study was approved by the Ethics Committee of the General Hospital of the Chinese People's Liberation Army (No. S2022-215-01). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that generative artificial intelligence (AI) and AI assisted technologies were not used in the writing process or any other process during the preparation of this manuscript.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

Data availability statement

Data was not generated for this case report. Additional information regarding the case can be requested from the corresponding author.

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