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RAPID COMMUNICATION

Salvage treatment in *IDH1* mutated acute lymphoblastic leukemia with venetoclax plus methotrexate and pegaspargase: A case report

Acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) are distinct subtypes of acute leukemia with respect to clinical and genetic features. Recently, ALLs were reported to share similar genes like *IDH1* mutations to AMLs.[1] Specifically, mutated *IDH1*(5%–15%) frequently occurs in AML and scarcely (1.9%) in ALL.[1] Notably, *IDH1* along with *SRSF2* mutation often exists in secondary AML patients and confers a poor prognosis. Recently, venetoclax (VEN) has been demonstrated extremely effective in combination with a hypomethylating agent or chemotherapy for *IDH1* mutated AML patients. However, whether VEN combining chemotherapy is effective among ALL patients with similar genetic features to AML remains unclear. Here, we successfully rescued a relapsed ALL case with *IDH1* mutation by VEN plus methotrexate and pegaspargase based on their antimetabolic pathways.

A 60-year-old male patient was diagnosed with B-cell ALL with 82% blasts (Fig. S1A), moderate anemia (hemoglobin of 85 g/L), mild thrombocytopenia (platelets of 107×10^9/L), and normal white blood cell count (4×10^9/L). Karyotyping showed 46, XY. The common B-cell phenotype was shown in Figure S2 and Figure 1A. Next-generation sequencing (NGS) indicated a missense mutation in *IDH1* R132S (32.46%) and a frameshift mutation in *SRSF2* K172 (19.36%). He achieved complete response (CR) after one cycle of the VDCLP regimen (Fig. 1B). After the early stage (CAM, HD-MTX-L-Asp, and MA) and late-stage consolidation therapies (VDLP, COATD, HD-MTX-L-Asp, and TA) according to CALLG2008 protocol, he developed a relapsed disease and presented with 26% blasts in bone marrow (Fig. S1B). These relapsed blasts increased the expression of leukemic stem cell markers like CD117, CD34, and TDT, suggesting relapsed blasts are arrested at an early progenitor stage (Fig. 1A; Fig. S3). At that time, his karyotyping was still normal. The variant allele frequency (VAF) of *IDH1* R132S mutated clone was 17% while *SRSF2* mutation disappeared. Because this patient relapsed within one year of chemotherapy, his prognosis should be adverse and the salvage treatment is possible only if a new scheme is adopted. In order to design the optional regimen for this relapsed patient, we conducted metabonomics analysis by Q300 Kit (Metabo-Profile, Shanghai, China) using plasma samples at the time of disease diagnosis and disease relapse. As a result, we found 15 up-regulated and 12 down-regulated metabolites (fold change >1 and P value < 0.05; Fig. 1C and Table S1) were significantly enriched in the KEGG pathways like valine, leucine, and isoleucine degradation, alanine, aspartate and glutamate metabolism, and cysteine and methionine metabolism, *etc* (Fig. S4). These findings demonstrate that amino acid metabolism is substantially more active in relapsed samples and suggest amino acids are essential for OXPHOS in relapsed blasts. Based on this result, we searched for the available drugs to design the treatment schedule (Fig. 1D). Generally, leukemia stem cells (LSCs), which cause refractory and relapsed diseases, prefer absorbing glutamine and branched-chain amino acids (BCAAs) to produce energies.[2,3] In this study, we found glutamine and BCAAs concentrations were significantly higher for this patient at disease relapse than at disease diagnosis. Notably, VEN inhibits glutamine uptake, resulting in a decrease in ATP production for LSCs' survival. Besides, VEN combined with the asparaginase (pegcrisantaspase) treatment shows synergistic anti-leukemic activity by depleting plasma glutamine.[4] Thus, VEN combined with asparaginase was first selected by us as an optional regimen for this patient. Secondly, asparaginase is an enzyme that breaks down asparagines, leading to stopping ALL cells to use asparagine as

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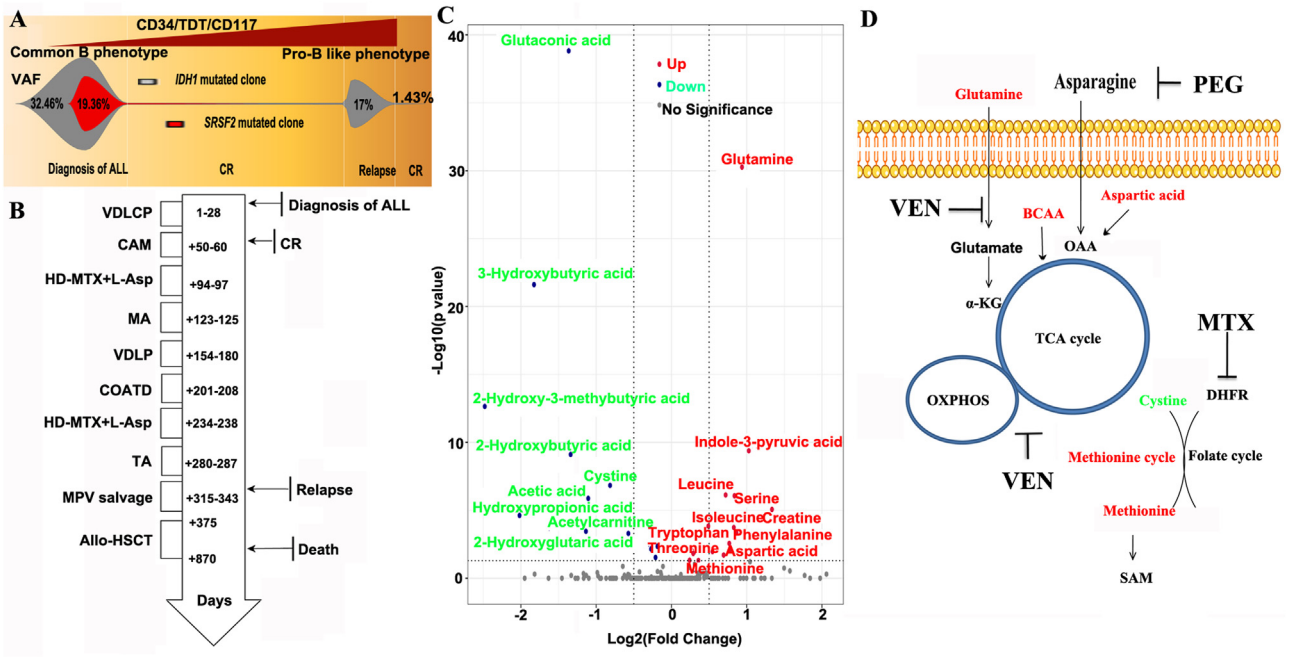

Figure 1 MPV salvage therapy for *IDH1* mutated ALL based on metabolic changes between disease diagnosis and relapse. Relapsed blasts increased the expression of leukemic stem cell markers like CD34, CD117, and TDT, implying the common-B-ALL regression to pro-B-ALL phenotype **(A)**. Schematic of a possible model of clone evolution inferred from next-generation sequencing data. *SRSF2* mutated subclone disappeared but *IDH1* mutated clone sharply reduced after induction treatment. *IDH1* mutated clone reoccurred at the time of disease relapse and decreased again after MPV salvage **(A)**. VAF, variant allele frequency. The treatment flowchart in this study was illustrated **(B)**. CALLG2008 protocol was a published protocol designed by the Chinese Acute Lymphoblastic Leukemia Cooperative Group for adult ALL. VDLCP: vindesine, 4 mg/d, intravenously, once on day 1, day 8, day 15, and day 22; daunorubicin, 40 mg/(m^2/d), intravenously, once on days 1—3; L-asparaginase 6,000 IU/m^2, subcutaneously, once on day 1; cyclophosphamide, 750 mg, intravenously, once on day 1; prednisone, 1 mg/(m^2/d), orally, once on days 1—14, days 15—28 (1/3 dose). CAM: cyclophosphamide, 750 mg/m^2, intravenously, once on day 1 and day 8; cytarabine, 100 mg/(m^2/d), intravenously, once on days 1—3 and days 8—10; mercaptopurine, 60 mg/(m^2/d), orally, once on days 1—7. HD-MTX + L-Asp: methotrexate, 3 g/m^2, intravenously, once on day 1; L-asparaginase 6,000 IU/m^2, subcutaneously, once on day 3 and day 4. MA: mitoxantrone, 8 mg/(m^2/d), intravenously, once on days 1—3; cytarabine, 750 mg/m^2, intravenously, twice on days 1—3. VDLP: vindesine: 4 mg/d, intravenously, once on day 1, day 8, day 15, and day 22; daunorubicin, 40 mg/(m^2/d), intravenously, once on days 1—3; L-asparaginase 6,000 IU/m^2, subcutaneously, once on day 11, day 14, day 17, day 20, day 23, and day 26; dexamethasone, 8 mg/(m^2/d), orally, once on days 1—7 and days 15—21. COATD: cyclophosphamide, 750 mg/m^2, intravenously, once on day 1; vindesine: 4 mg/d, intravenously, once on day 1; cytarabine, 100 mg/m^2, intravenously, once on days 1—7; teniposide, 100 mg/(m^2/d), intravenously, once on days 1—4; dexamethasone, 6 mg/(m^2/d), orally, once on days 1—7; TA: teniposide, 100 mg/(m^2/d), intravenously, once on days 1—4; cytarabine, 100 mg/m^2, intravenously, once on days 1—7. Plasma metabolites changed between the relapsed sample and diagnosed sample. Red color letters represent increased concentrations of metabolites, and green colors indicate decreased concentrations of metabolites in relapsed samples **(C)**. The antimetabolic mechanisms of venetoclax, methotrexate, and pegaspargase against relapsed ALL in this study **(D)**. VEN inhibits amino acid uptake and oxidative phosphorylation; methotrexate reduces S-adenosyl methionine (SAM) for DNA methylation; pegaspargase stops ALL blasts to use asparagines as energies.

energy. High asparagine levels can form protective niches for leukemia cells and confer L-asparaginase resistance to ALL.[5] In this study, there is no difference in asparagine concentration between the relapsed and diagnosed samples; although aspartic acid levels were higher in the relapsed sample than those in the diagnosed sample. In fact, it was previously reported that high aspartic acid was seen during induction therapy containing asparaginase agents against ALL. Thus, there is no evidence for the increased asparagine synthesis in the relapsed sample, and pegaspargase (a pegylated conjugate of L-asparaginase) can be still selected as a potentially effective drug. Finally, methotrexate reduces intracellular pools of 5-methyltetrahydrofolate, decreases the conversion of cysteine to methionine, and interferes with DNA methylation. Additionally, high-dose intravenous methotrexate is proven as an effective chemodrug against ALL. Therefore, we designed the treatment regimen based on their antineoplastic and antimetabolite properties and named it the MPV regimen [methotrexate, 3 g/m^2, intravenously, once on day 1; pegaspargase 3,750 IU, subcutaneously, once on day 2; VEN, orally, once daily (100 mg on day 1, 200 mg on day 2, and 400 mg on days 3—28)]. As expected, he achieved CR again after the above salvage therapy. Bone marrow smear and blood test demonstrated CR. NGS analysis reported the VAF of *IDH1* R132S mutation was reduced to 1.43%. Immediately, the

treatment was shifted to allogeneic hematopoietic stem cell transplantation (HSCT). Unfortunately, this patient passed away after one year of HSCT due to pulmonary aspergillosis.

In summary, we provided a salvage regimen of VEN-based chemotherapy for *IDH1* mutated ALL patients. This study needs to be further validated in another large cohort of patients.

Conflict of interests

The authors declare no conflict of interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2023.02.011.

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