ALL-389

soho2023
ELEVENTH ANNUAL MEETING

Venetoclax in the Treatment of Relapsed Refractory Early T cell Precursor ALL (ETP-ALL). Case Series and Review of the Literature

Mahmoud Hasaneen MD[1], Fatima Khadadah MD[1], Ramesh Pandita MD[1], Rasha Ghonema MD[1], Mohan Ram MD[1], Salem Alshemmari MD[1,2], Abdulaziz Hamadah MD[1], Anita Kunhikrishnan MD[1], Dina Ismail Abd El Razik MD[1], Ahmad Alhuraiji MD[1]

[1]Kuwait Cancer Control Center, Sabah Health Region Kuwait; [2]Kuwait University, Kuwait

مركز الكويت لمكافحة السرطان
Kuwait Cancer Control Center

INTRODUCTION

ETP-ALL is a high-risk subgroup of ALL characterized by early differentiation arrest and distinct genetic and transcriptional features. ETP-ALL represents 10% to 30% of T-cell ALL (T-ALL) cases in adults and 10% to 15% of cases in children and exhibits inferior response rates to chemotherapy with treatment refractoriness & high rates of relapse leading to dismal outcomes.

CASE 1

A 30 year old man was diagnosed with ETP-ALL in December 2022. BM was consistent with ETP-ALL with 60 % blasts (Fig.1) expressing CD99, CD7, CD13, CD33, cCD3, HLA-DR and TdT. CT chest revealed a large 8 cm mass encasing the mediastinal vessels/bronchi. Karyotyping was 46,XY with BCR-ABL1 & 14q11 negative FISH & molecular testing showed WT1 P376*(VAF 25.14%) and RUNX1 R320*(VAF 24%). Post induction with DFCI, BM showed 20% lymphoblast (Fig.2). He was salvaged with Hyper-CVAD + 7 days of venetoclax which he tolerated well. Patient achieved a CR (Fig.3) with negative MRD by 8-colour multi parameter flow cytometry. He received 3 cycles in total & was referred for allogenic stem cell transplantation as he has a fully matched sibling donor.

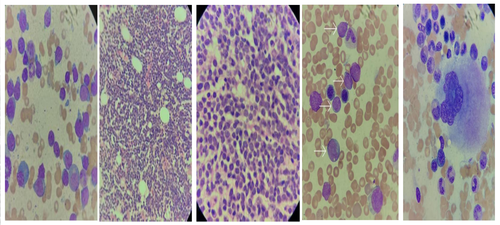
CASE 2

A 29 year old man was diagnosed with T-ALL in January 2020 with 89 % BM blasts. He was treated with Hyper-CVAD and achieved a CR following induction. He completed maintenance treatment in August 2022. BM evaluation post treatment was in CR, MRD negative, CSF negative. He relapsed on 23/3/2023 with 10% blasts in BM (Fig.4). Flowcytometry was positive for cCD3, CD7, CD33 & TdT but negative for HLA-DR. Karyotype - 46,XY & negative NGS.

In May 2023 he was induced with FLAG-Mitoxantrone. BM D28 revealed refractory disease with 66% blast (Fig.5). Flowcytometry (with extended T-cell markers) was positive for cCd 3, CD2, CD7 CD33, TDT, while negative for CD5 and CD1a. Karyotype 46,XY, with 20 metaphases analyzed, with negative NGS. In view of ETP-ALL not in remission, he was started on Mini-CVD + venetoclax in July 2023. He achieved a flow MRD negative CR (Fig.6). He finished cycle Ib and will proceed to allogenic transplant from his fully matched brother.

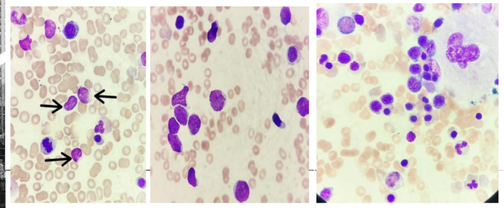
FIGURES

Fig.1 Fig.2 Fig.3



CASE 1

Fig.4 Fig.5 Fig.6



CASE 2

CONCLUSIONS

Clinical experience of venetoclax in ALL is still emerging, but the current available data support the hypothesis of BH3-mimetic activity in ALL. Venetoclax-containing regimens are relatively safe and can achieve deep responses, although these are frequently transient, they should be utilized as a bridge to all-SCT in eligible patients.

DISCUSSION

Venetoclax is a selective BH3 mimetic inhibitor of BCL2, an anti-apoptotic protein conferring enhanced survival in leukemia cells including CLL, AML and ALL.

Preclinical studies demonstrate that BCL-2 family proteins play a significant role in ALL blasts, including early leukemia initiation stages. Certain molecular subtypes such as MLL-rearranged “t(4;11)”, TCF3-HLF t(17;19) and hypodiploid are correlated with BCL-2 overexpression, with preclinical evidence supporting the use of venetoclax in these subtypes.

ETP-ALL is more dependent on BCL-2 and shows sensitivity to venetoclax. Preliminary studies of venetoclax added to mini-hyper-CVD showed encouraging results, including in the relapse/refractory setting.

We found 165 cases reported in 8 studies between 2019 and 2022 on the use of venetoclax with different chemotherapeutics in ALL with promising results which are summarized in table 1.

REFERENCES

Jain, N.; et al. **2019.** Richard-Carpentier, G.; et al. **2020**. Venugopal, S.; et al. **2021**. Wang, H.; et al. **2022**.

CONTACT INFORMATION

Ahmad Alhuraiji, Department of hematology, Kuwait Cancer Control Center. aalhuraiji@moh.gov.kw
Mahmoud Hasaneen, Department of hematology, Kuwait Cancer Control Center. mabdelmaged@hotmail.com

ABBREVIATIONS

ETP-ALL: Early T cell precursor Acute Lymphoblastic Leukemia, Hyper-CVAD: with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone,FISH : Fluorescent in situ Hybridization, MRD: Mesurable residual disease, BM: Bone Marrow, cCD3: cytoplasmic CD3, CR: Complete Remission, NGS: Next Generation Sequencing,BMT: Bone Marrow Transplantation, CLL: chronic lymphocytic leukemia, AML: acute myeloid leukemia, MLL: Mixed-Lineage Leukemia gene.

Table 1

Author, Year	Cohort	Design, Regimen	ORR	OS	Grade III/IV AE
Jain 2019	n = 18 Ph-neg ALL > 18 yo r/r or > 60 yo ND	Phase 1, Ven 400/600 mg with mini-hyper-CVD	r/r: 37.5% ND: 100 %		39% FN, 17% hyperglycemia, 11% hypocalcemia, 1 pneumonia, 1 sepsis
Carpentier 2019	n = 13 r/r T-ALL Adults	Retrospective, Ven 100–400 mg with chemotherapy/HMA	60 %	7.7 mo	Prolonged cytopenia (percentage not reported)
Venugopal 2021	n = 23 Ph-neg ALL > 18 yo r/r or > 60 yo ND	Phase 2, Ven 400 mg with mini-hyper-CVD	65 %	7.1 mo	Cytopenia (percentage not reported), 1 sepsis
Gibson 2021	n = 18 ALL age < 22	Retrospective, Ven 400 mg with chemotherapy	61 %		89% thrombocytopenia, 53% neutropenia, 22% hyperbilirubinemia, 28% sepsis, 28% FN, 1 pneumonia, 1 coagulopathy, 1 mucosal Infection
Pullarkat 2021	n = 47 r/r ALL, all ages	Phase 1, Ven + navitoclax with Chemotherapy	59.6 %	7.8 mo	46.8% FN, 38.3% neutropenia, 25.5% Thrombocytopenia
Palmisiano 2021	n = 18 r/r Ph-neg ALL adults	Phase 1, Ven + L-vincristine	44 %		67% neutropenia, 56% leukopenia, 50% anemia, 1 TLS
Short 2021	n = 9 r/r Ph(+) ALL adults	Phase 1, Ven + ponatinib + dex	56 %		44% cytopenia
Wang 2022	n = 19 r/r Ph(+) ALL adults	Retrospective, Ven + ponatinib + dex	89.5 %	400 days	73% neutropenia, 36% anemia, 52% thrombocytopenia

n—number of patients; Ph-neg—Philadelphia chromosome-negative; ALL—acute lymphoblastic leukemia; yo-years old; r/r-relapsed/refractory; ND—newly diagnosed; Ven—venetoclax; CVD—cyclophosphamide, vincristine and dexamethasone; HMA—hypomethylating agent; dex—dexamethasone; ORR—overall response rate; OS—overall survival; mo—months; AE—adverse event; FN—febrile neutropenia.