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Atypical immunogenetic and molecular characteristics of a 15-Years-Old male affected by ETP-ALL (Early T-precursor acute lymphoblastic leukemia)

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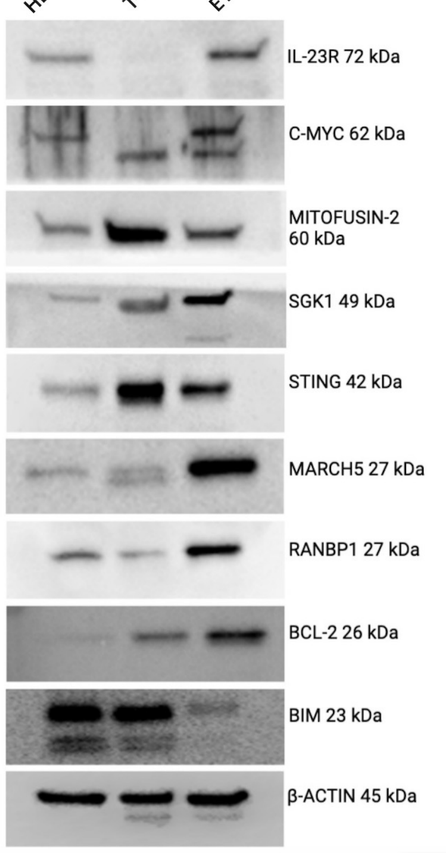
INTRODUCTION & AIM

ETP-ALL (Early T-cell precursor acute lymphoblastic leukemia) is a recently recognized high-risk T lymphoblastic leukemia subgroup with poor long-term outcomes. ETP-ALL cells are endowed with peculiar immunophenotypic and genotypic traits, interpolating between the myeloid and lymphoid lineages.The diagnosis of ETP is primarily based on immunophenotypic markers including positive cytoplasmic CD3 and CD7, negative CD1a and CD8, low or absence of CD5, and some positive myeloid lineage markers[1;2].
ETP-ALL is also known for its complex karyotype and high genomic instability.
Recently, BCL2 over-expression has been reported in selected ETP-ALL cases, thus suggesting a potential application for the BCL2-inhibitor ***venetoclax***. However, the impact of the BCL2 pathway in ETP-ALL biology remains poorly understood, and the use of ***venetoclax*** is occasional and still lacks standardization in guidelines[3;4].

We demonstrate for the first time novel genetic changes occurring during disease course and driving blast expansion in a BCL2-dependent manner, which is not observed at diagnosis. Additionally, an *ex-vivo* assay established using primary blasts confirms the sensitivity to ***venetoclax***, strengthening patient's cytogenetics findings and sub-clinical response. Taken together, the combination of cytogenetics, molecular and clinical findings demonstrated the acquisition of a BCL2-dependency during disease progression, which provides the basis for BCL2-targeted therapies in ETP patients.

RESULTS & DISCUSSION

1A

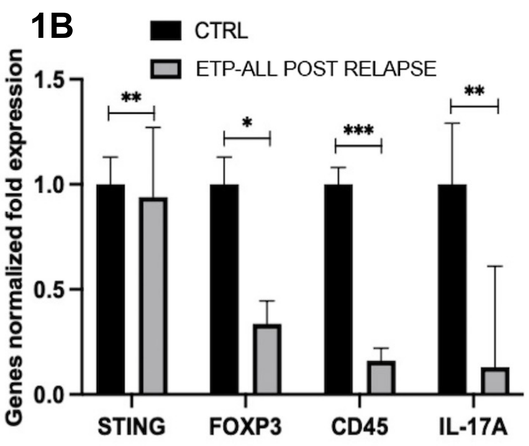


We compared ETP-ALL, classical T ALL and subject without any pathology. As expected (Fig. 1A), BCL2 was found to be significantly higher compared to the typical T leukemia and control sample, while the levels of Mitofusin-2 (MFN2), a protein involved in BCL2 breakdown, is downregulated in ETP; moreover, we observed an upregulation in MARCH5, a protein that inhibits MFN2 and is positively correlated with BCL2. As a result, c-MYC levels dramatically increased while BIM, a pro-apoptotic factor of BCL2 family, was completely suppressed. Altogether, these data indicate a complete shift towards pro-blastic deregulation accompanied by a BCL2-dependent regulatory pathway. We observed a significant increase in IL23R, SGK1, and RANBP1 compared to neoplastic and non-neoplastic controls (Fig. 1A)

major chromosome aberrations	relative frequency (%)
Complete numerical aneuoploidies	27.2%
Chromosome 4 long arm (q) deletion or complete chr. 4 del	100%
16;18(der) unbalanced translocation	18.18%
Other mixed complex karyotypes	81.8%

relative frequency of the key observed anomalies

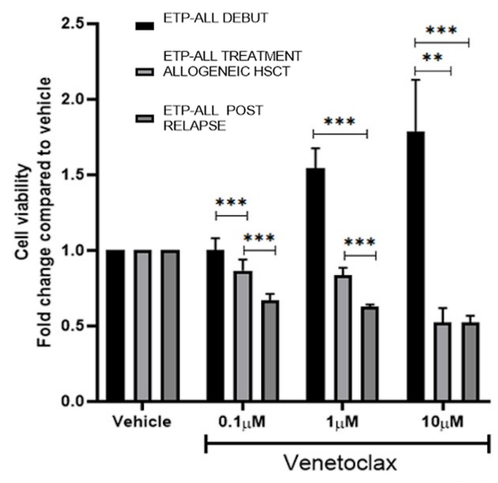
1B



Transcript levels of the examined markers revealing down-regulation of FOXP3, CD45, IL-17A(Fig. 1B). These data indicate that T lymphocytes in the blastic component may adopt a pro-inflammatory phenotype, leading to resistance and positive selection.

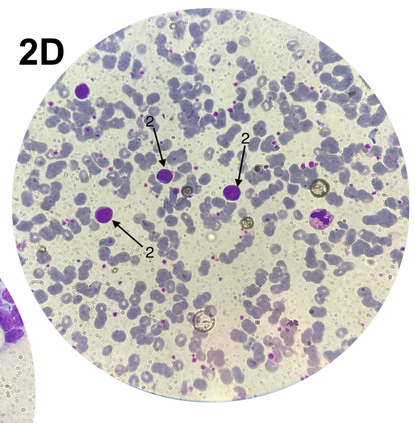
RESULTS & DISCUSSION

2A

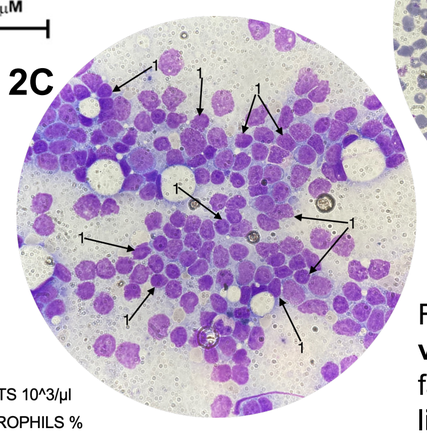


Ex vivo assays were conducted on bone marrow lymphocytes from the subject at 3 different phases: ETP-ALL debut, post-allogeneic HSCT and relapse. This revealed that initially lymphocytes exhibit complete complete resistance to high doses of **venetoclax**, while sensitivity to the drug started to develop after allogeneic HSCT, reaching a peak, even at low doses, during the relapse phase(Fig. 2A)

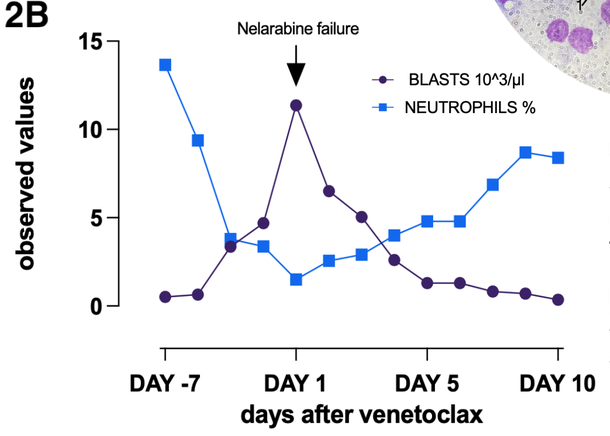
2D



2C

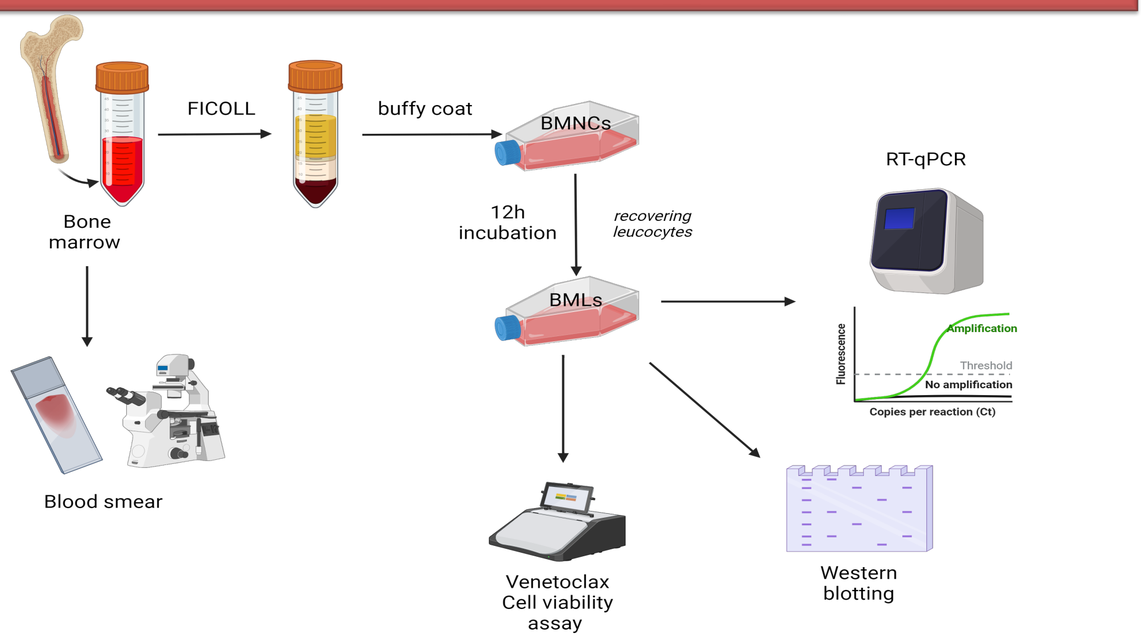


2B



Following 10 days of **venetoclax** treatment, after failures of first- and second-line salvage therapies (AIEOP-BFM ALL 2017 and nelarabine) a significant decrease in blasts and a return of neutrophils can be observed(Fig. 2B) The *pre*-venetoclax blood smear shows the presence of a carpet of leukemic blasts (Fig. 2C) while the *post*-venetoclax smear (Fig. 2D) shows the absence of leukemic blasts.

METHOD



CONCLUSION

In summary, our data underscore the need to evaluate the mechanisms involved in the overexpression of BCL2 and associated proteins as well as the immunological microenvironment in the context of leukemia. Our findings provides the rationale for **venetoclax** as a viable therapeutic option in the relapsed form of the disease due of its close BCL2-dependence. In addition, our results may contribute to the development of a new set of markers with therapeutic and prognostic significance in ETP-ALL.

REFERENCES

1. Mao, J et al. 2021 doi:10.2147/OTT.S312494
2. Jain, N. et al. 2016 doi:10.1182/blood-2015-08-661702.
3. Arber, D.A et al. 2016 doi:10.1182/blood-2016-03-643544.
4. Zhang, J. et al. doi:10.1038/nature10725.

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