Daratumumab efficacy in T-ALL Two Clinical Cases

Marco Cerrano , Barbara Castella, Giuseppe Lia, Lucia Brunello, Sara Butera, Matilde Scaldaferri, Massimo Massaia, Mario Boccadoro, Dario Ferrero, Benedetto Bruno and Luisa Giaccone

Division of Hematology, University of Turin - A.O.U. Città della Salute e della Scienza di Torino, Turin, Italy

INTRODUCTION

- In preclinical studies, the anti-CD38 antibody daratumumab (DARA) demonstrated significant activity in T-ALL [1,2,3]
- However, only a few relapsed or measurable residual disease (MRD) positive patients responding to DARA have been reported so far [4,5,6]
- A multifaceted immunomodulatory role of DARA through the eradication of CD38-pos immune suppressor cells has been demonstrated in Myeloma, but no data exists in T-ALL

PATIENTS and METHODS

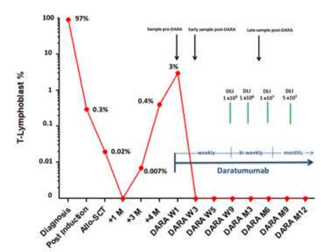
- We describe two relapsed/MRD positive T-ALL patients treated with DARA
- Both lacked IG-TCR rearrangements for PCR monitoring of MRD, which was assessed by flow cytometry only
- To explore the immunomodulatory effects of DARA, extensive immune cell phenotyping and quantification was performed on mononuclear cells using validated multifluorochrome antibody panels, including α-CD38 multi-epitope FITC. Analysis were performed using FACS Calibur flow cytometers, and data were analyzed using FlowJo software. Functional assays were employed to assess the granzyme and perforin cytotoxic molecules in T cells

Characteristic at diagnosis	Patient 1	Patient 2
Age at diagnosis (years)	44	25
Sex	Male	Male
CNS involvement	No	Yes
Extramedullary involveme	No	Yes
WBC (10^9/L)	26.7	31.9
Hb (mg/dl)	3.9	12.1
Platelets (10^9/L)	4	29
BM blasts (%)	97	40
PB blasts (%)	93	20
LDH (U/L)	1116	1062
Immunophenotype (positi	cCD3/CD7/dimCD5/CD13/CD34/ CD33/CD11b/CD117/HLADR/CD38	cCD3/CD7/dimCD5/CD13/ CD99/CD10/CD38
Karyotype	Complex karyotype (71-76 XXYY<4n>, +1,+3, +4, del(3)(q12q33), +11, +14, +17, +20, +21, +22)	46 XY, i(9)(q11qter)
First-line treatment		
Chemotherapy regimen	According to GIMEMA LAL1913	According to GIMEMA LAL1913
Consolidation with AlloHSC	Yes	No
Time from diagnosis to dara	9	8
Characteristic at relapse		
BM blasts (%)	3 (LAIP)	1.4 (LAIP)
CNS involvement	No	No
Extramedullary involveme	No	Yes
Immunophenotype (positi	cCD3/CD7/CD13/CD34/ CD11b/CD117/CD38	cCD3/CD7/dimCD5/CD13/ CD99/CD10/CD38

RESULTS

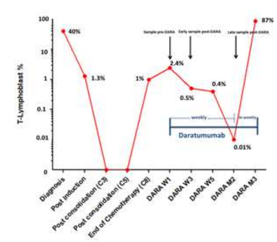
PATIENT 1

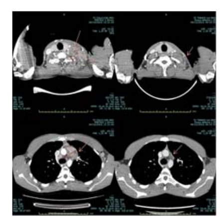
- He was diagnosed in March 2018 and achieved CR without MRD negativity
- After TBI-based myeloablative allo-SCT from his haploidentical sister, MRD became negative, but reappeared at 3 months. Despite discontinuation of immunosuppressors, MRD raised to 3%
- In December 2018, he was started on DARA and MRD negativity was obtained after 2 weekly infusions. He remained on DARA and escalating dose of DLI were commenced; after the last dose he developed severe cGvHD, responsive to therapy
- Fifteen months after DARA start and a total of 14 infusions, he remains in MRD-negative CR and he is tapering GvHD treatment



PATIENT 2

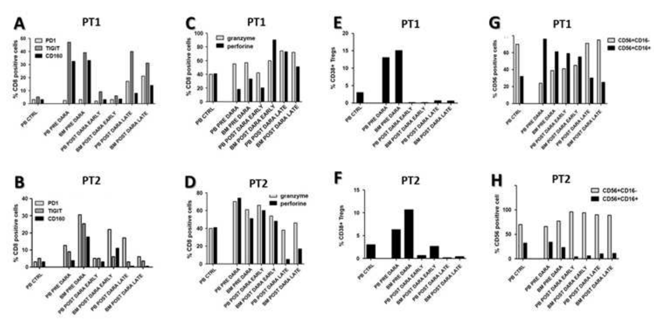
- He was diagnosed in December 2018 and achieved CR and MRD negativity
- He was not eligible for allo-SCT, thus he was continued on chemotherapy
- At the end of the last block, he become MRD positive and CT scan revealed multiple lymphadenopathies, positive for T-ALL relapse (biopsy)
- He was started on DARA and, in less than 2 months, pathological lymphadenopathies disappeared. MRD slowly decreased over time but it never became negative
- Three months after DARA start, he relapsed with 87% of T-lymphoblasts in the BM, without extramedullary involvement





IMMUNOMODULATORY EFFECTS

- **Expression of exhaustion/senescence marker**. CD160 expression persistently decreased after DARA; TIGIT marked drop early and was persistent in patient 2 (PT2). PD-1 reduction occurred PT2 only, **Fig A/B**
- **T-cell activation and functionality**. Persistent increase in perforins expression in CD8 T cells in PT1 after DARA , diminished in PT2, **Fig C/D**
- **Activity on immunosuppressive populations**. Subpopulation of peripheral Tregs (CD4+CD25+CD127dim) strongly and persistently reduced, **Fig E/F**
- **NK cell subsets.** NK persistently reduced after DARA; the expression of the activation marker CD69 was upregulated. Increase of the proliferative subset (CD56+CD16-), and reduction of the cytotoxic one (CD56+CD16), **Fig G/H**



CONCLUSIONS

- DARA showed significant activity in two cases of relapsed/MRD-positive T-ALL, which was persistent in the case with MRD positivity post allo-SCT
- DARA eradicated immune suppressor cells and allowed helper and cytotoxic T cell to expand, thus leading to better host-anti-tumor immune response
- These findings confirm the potential clinical benefit of DARA in T-ALL and could hint at its immunological mechanism of action, possibly contributing to the design of bigger studies and to future developments in this setting

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CONTACT: Marco Cerrano: cerranomarco@gmail.com

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