Low Dose Rituximab Efficiently Clears Circulating CLL Cells and Maintains Sensitivity to Antibody Dependent Cellular Phagocytosis (ADCP)

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Introduction

1. High frequency (2 x week), low dose (50 mg) (HFLD) rituximab (RTX) and acalabrutinib is highly effective initial therapy for patients (n=38) with progressive CLL[1,2]
2. First dose of 50 mg IV RTX administered at 25 mg/h:[3]
   - Circulating CLL cell count decreased 84% at 1h. No additional change at end of initial infusion (**Fig. 1**).
   - Median CLL cell membrane CD20 levels decreased to 65% at 1h and 41% at the end of infusion.
   - Median serum RTX concentration 2 mcg/ml at 1h and 10 mcg/ml at end of infusion.
   - Median complement (CH50) concentration decreased to 91% at 1h and to 81% at end of the infusion.

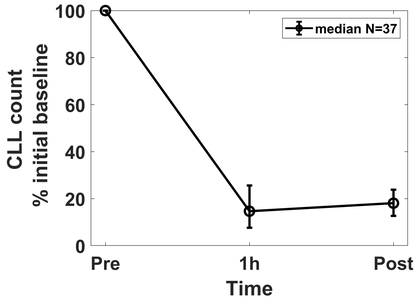

Fig 1: CLL Cell count
Median with 95% Confidence Interval

Hypothesis

The clearance of circulating CLL cells is limited by resistance of residual circulating CLL cells to RTX induced ADCP.

Methods

Blood specimens from 13 patients were sampled prior to starting therapy (C1D1_pre), at 1h after start of IV RTX infusion (C1D1_1h), at the end of infusion (C1D1_post), and 48h after initiation of therapy (C1D3_pre) (**Fig. 2**).

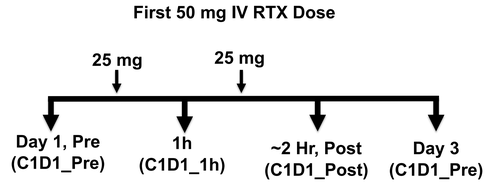

Fig 2: Sample Time Points

ADCP measured by live cell time-lapse, high-content microscopy imaging of phagocytosis of CLL cells by human monocyte-derived macrophages and quantified as the area under the curve (AUC) of the void index (**Fig. 3**).[4]

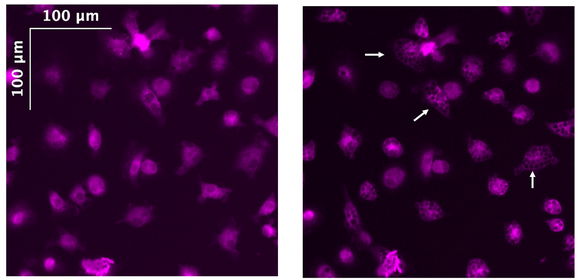

Fig. 3 ADCP Co-culture at time 0 (A) and 3 h (B)

Results

Circulating CLL cells sampled after in vivo treatment with RTX are sensitive to in vitro RTX or alemtuzumab mediated macrophage ADCP (Wilcoxon Match-Paired test; all p > 0.05) (**Fig. 4**).

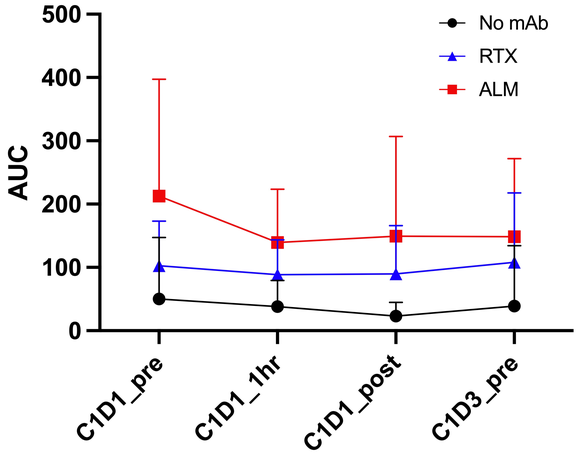

Fig 4: Median Void Index AUC
n=13
Each time point compared to C1D1_pre all p>0.05.

Conclusions

- <25 mg IV RTX decreases CLL cell count ~80% in <1h.
- No change in CLL count after the first hour of infusion.
- CLL cell clearance is not limited by:
  - RTX concentration
  - CD20 levels
  - Complement
- Residual circulating CLL sensitive to in vitro ADCP.
  - Supports null hypothesis
- No evidence of CLL cell sequestration.[2]

Discussion

- New hypotheses:
  - IV RTX rapidly induces CLL cell clearance by fixed macrophage ADCP.
  - Clearance decreased by innate immune "exhaustion."
- Data similar to published descriptions of macrophage hypophagia in vitro (primary human cell studies) and in murine models.[5]

References

1. ClinicalTrials.gov, NCT03788291
2. Wallace et al Blood Adv 2023 PMID: 36689726
3. Moore et al Leuk Res 2023 PMID: 37003030
4. Chu et al J Cell Sci 2020 PMID: 32005699
5. Pinney et al Blood 2020 PMID: 32556153

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