Treatment Strategies and Outcomes for Double Refractory chronic lymphocytic leukemia; A single center experience

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Background

There remains an unmet need for patients with aggressive disease refractory to both Bruton Tyrosine kinase inhibitors (BTKi) and Venetoclax. We conducted a single-center retrospective study to identify the treatment strategies and outcomes for these 'double refractory' patients.

Methods

The data was gathered using the pharmacy dispensing records. All patients with CLL that filled a Venetoclax prescription from the in-house Pharmacy at the H. Lee Moffitt Cancer & Research Institute from 2016-2021 were identified. The medical record charts of these patients were accessed to determine double-refractory patients who had progression of disease (POD) while on BTKi followed by Venetoclax-based therapy or vice-versa. Only patients with POD were selected. Patients who had their treatment regimen changed due to intolerance or adverse effects were not included. The Patient's charts were followed till January 1st,2023. The Mantel-Cox test was used to determine differences in survival outcomes among various cohorts. A p-value of ≤0.05 was considered significant.

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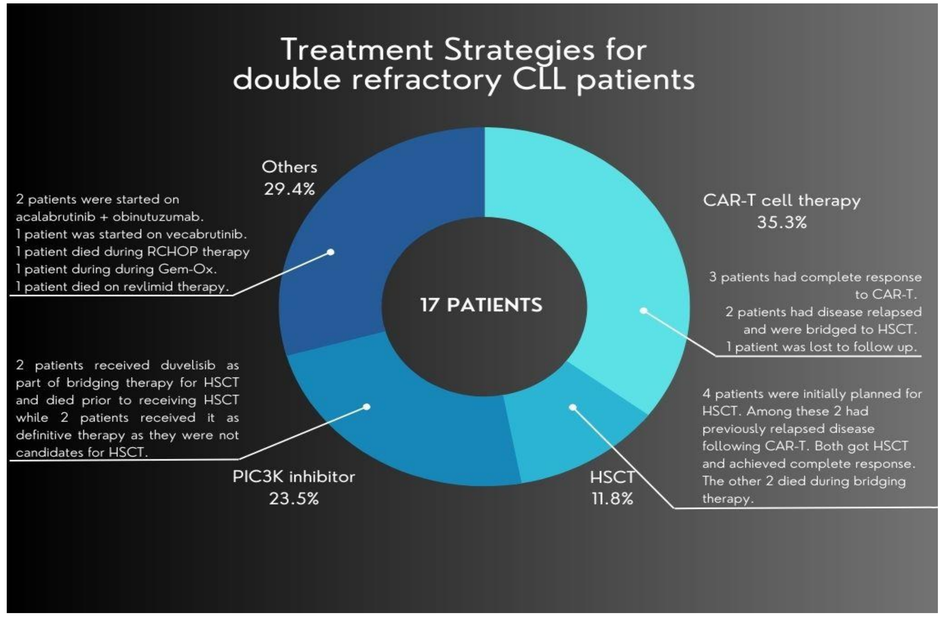
Results

- A total of 17 double refractory CLL patients were identified between 2016 to 2021.
- Fifteen (88.2%) patients had unmutated IgHV disease, 11 (64.7%) had 17p deletion
- Nine (52.9%) patients had complex karyotype.
- Seven (41.2%) patients had BTK mutation.
- The median lines of therapies prior to Venetoclax was 3 (range 1-7).
- Seven (41.2%) patients had Richter's transformation during their disease course.
- Six patients (35.3%) were bridged to chimeric T cell therapy (CAR-T) following double refractory status. Patient characteristics described in the table.
- Among these, 2 patients relapsed and eventually needed to be bridged to HSCT.
- The overall survival of patients that received CAR-T cell therapy was significantly better (median 33 months versus 6 months, p = 0.05)



Age	IgHV status	Cytogenetics	Mutational Status	Treatment History	Best Response to CAR-T	Follow up time (months)	Death during follow up period
67/F	Unmutated	Del 17p	CDKN2B, FXW7, KRAS, NF1, TP53, ZFHX4	Ibrutinib→ Richter's transformation→ DA-EPOCH→Ibrutinib + Venetoclax→ **Tisagenleleucel** +Ibrutinib→ POD→pembrolizumab→POD→ GDP + Rituximab + local XRT→Death	Complete response	5	Yes
66/F	Unmutated	Del 11q Del 13q Del 17p Trisomy 13	BTK C481R, EBRR2, KLF2, FLT1, TP53, TSC1	Ibrutinib→POD→Ofatumumab/ Obinutizumab + Venetoclax→ Richter's transformation→R-CHOP + Ibrutinib→ allogeneic CAR-T→**Tisagenleleucel**→POD→acalabrutinib bridged to HSCT	Partial Response	38	No
57/F	Unmutated	Del 11q Del 13q Del 17p	MUTYH, SF3B1, TP53, TNFAIP3	FCR→Ofatumumab + lenalidomide→POD→Ibrutinib→POD→Venetoclax + ibrutinib→ POD→ **KTE-X19**	Complete Response	33	No
69/F	Unmutated	Del 13p Del 17p	BTK C481 R, BTK C481F, TP53, ATM, MAP2K1, MUTYH	Obinutuzumab→(Rituximab + Bendamustine) + Ibrutinib maintenance→POD→Venetoclax→POD→ Vecabrutinib→POD→Obinutuzumab +Ibrutinib→Venetoclax→**JCAR017**	Unknown	7	No
47/F	Unmutated	Del 13p Del 17p	IKZF3, SF3B1, TP53, PLCg2	Chlorambucil→POD→Bendamustine→POD→ FCR→ HSCT→Ibrutinib + Venetoclax→Richter's transformation→ RCHOP → **Lisocabtagene maraleucel→ Death**	Complete response	13	Yes
54/F	Unmutated	Del 11p Del 13p Del 17p	BTK C481S, BCL V156D, EPHA7, TP53	FCR→POD→Bendamustine→Ibrutinib→POD→Ibrutinib + Venetoclax→**KTE-X19**→Venetoclax→POD→Duvelisib bridged to HSCT	No response	26	No

- Overall, 3 patients had a complete response as the best response to CAR-T.
- Four patients (23.5%) were started on phosphoinositide 3 kinase (PI3-K) inhibitor
- Both patients that received HSCT had previously relapsed on CAR-T cell therapy.
- Two patients received acalabrutinib and obinutuzumab.
- One patient was started on vecabrutinib and died due to POD.
- Two patients died while on chemotherapy due to Richter's transformation
- One patient was started on lenalidomide and died during the follow-up period

Conclusion

The patients in our small cohort that received CAR-T cell therapy had significantly longer survival. However, the benefit was likely driven by patients that received HSCT at disease relapse. As most patients with CLL are elderly and not eligible for transplant, treatment options for double refractory patients remain limited.