Abstract #1454

Clinical Outcomes of Patients with Epstein–Barr Virus-Driven Post-Transplant Lymphoproliferative Disease Following Hematopoietic Stem Cell Transplantation Who Fail Rituximab: A Multinational, Retrospective Chart Review Study

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BACKGROUND

- Post-transplant lymphoproliferative disease (PTLD) occurs following allogeneic hematopoietic stem cell transplantation (post-HCT) as a consequence of immunosuppression.
- In most cases following HCT, PTLD is associated with Epstein–Barr Virus (EBV) infection of B cells, either due to reactivation, or from primary EBV infection.[1–3]
- Clinical practice treatment guidelines recommend rituximab as preemptive therapy for EBV reactivation (based on EBV virus load) and for treatment of EBV-driven (EBV$^+$) PTLD following HCT.[3]
- For EBV$^+$ PTLD patients who fail initial therapy with rituximab there is no standard of care and limited treatment options exist. Failure of initial therapy after rituximab is associated with poor survival.
- Published evidence on the clinical outcomes for patients who fail rituximab is limited.

OBJECTIVE

- To describe the outcomes for patients diagnosed with EBV$^+$ PTLD following HCT who failed rituximab in a multinational real-world setting.

METHODS

- Data from a large multinational, multicenter retrospective chart review study of EBV$^+$ PTLD patients following HCT or solid organ transplant (SOT) who received rituximab or rituximab plus chemotherapy (CT) between January 2000–December 2018 and were refractory (failed to achieve complete response [CR] or partial response [PR]) or relapsed at any point after such therapy was utilized.
- A total of 29 centers across North America (United States and Canada) and the European Union contributed data to this study.
- Descriptive patient and disease characteristics were reported.
- The Kaplan-Meier (KM) method was used to estimate the overall survival (OS).
- OS was estimated from rituximab failure date, defined as the earliest date when patients became refractory or relapsed following rituximab ± CT to death, lost to follow-up, or the end of follow-up, whichever came first.
- Patients with primary CNS PTLD, Hodgkin, Burkitt lymphoma or peripheral T-cell lymphoma were excluded.

RESULTS

- A total of 81 patients were identified with median follow-up time of 1.7 months from the date of PTLD diagnosis. Patient characteristics at the time of transplant are summarized in **Table 1**.

Table 1. Patient Characteristics at Transplant

Median age at transplant, years (range)	48.7 (2–75)
	n (%)
Male	49 (60.5)
Initial diagnosis leading to HCT	
Acute lymphoblastic leukemia (ALL)	13 (16.0)
Acute myeloid leukemia (AML)	26 (32.1)
Aplastic anemia	5 (6.2)
Chronic lymphocytic leukemia (CLL)	4 (4.9)
Chronic myeloid leukemia (CML)	4 (4.9)
Multiple myeloma	1 (1.2)
Myelodysplastic syndromes (MDS)	7 (8.6)
Non-Hodgkin lymphoma (NHL)	4 (4.9)
Other	16 (19.8)
Missing	1 (1.2)
Primary disease status leading to HCT	
In remission	53 (65.4)
Not in remission	26 (32.1)
Unknown/Missing	2 (2.4)
Allograft donor type	
HLA-matched related donor (MRD)	10 (12.3)
HLA-matched unrelated donor (MUD)	33 (40.7)
Haploidentical	5 (6.2)
Mismatched related donor (MMRD)	3 (3.7)
Mismatched unrelated donor (MMUD)	27 (33.3)
Unknown	2 (2.5)
Stem cell source	
Bone marrow	9 (11.1)
Cord blood	21 (25.9)
Peripheral blood mononuclear cell (PBMC)	43 (53.1)
Unknown/Missing	8 (9.8)
Conditioning regimen used	
Myeloablative conditioning (MAC)	48 (59.3)
Reduced intensity conditioning (RIC)	30 (37.0)
Unknown/Missing	3 (3.7)

- Median age at PTLD diagnosis was 49 years (range: 2–75) and median time from transplant to PTLD was 3 months (range: 0.8–100.8 months) (**Table 2**). Almost 65% of the PTLD was reported as monomorphic histology and about 70% of the patients had extra-nodal disease.

Table 2. PTLD Characteristics

Median age at PTLD diagnosis, years (range)	49 (2–75)
Median time to PTLD onset from HCT, months (range)	3 (0.8–100.8)
Median follow-up time from PTLD diagnosis, months (range)	1.7 (0.03–107.6)
	n (%)
PTLD histology type	
Early lesions	2 (2.5)
Monomorphic	52 (64.2)
Diffuse large B-cell lymphoma (DLBCL)	46 (56.8)
Polymorphic	18 (22.2)
Unknown	9 (11.1)
PTLD stage	
Stage I & II	8 (9.8)
Stage III & IV	63 (77.8)
Unknown	10 (12.3)
PTLD onset	
Early PTLD (≤100 days from transplant)	44 (54.3)
Late PTLD (>100 days from transplant)	37 (45.7)
PTLD involved sites*	
Bone marrow	13 (16.0)
GI	14 (17.3)
Kidney	11 (13.6)
Liver	29 (35.8)
Lung	17 (21.0)
Lymph nodes	62 (76.5)
Spleen	23 (28.4)
Other	31 (38.3)
Unknown	1 (1.2)
Extra-nodal sites of PTLD	56 (69.1)
CD 20 status at diagnosis	
Positive	52 (64.2)
Negative	15 (18.5)
Unknown	14 (17.3)

*Not mutually exclusive groups

- Sixty-eight (84%) patients received rituximab monotherapy and 13 (16%) received rituximab plus CT as initial therapy.
- 45 patients received no further treatment after failure to rituximab ± CT and 36 received next line of therapy, with CT containing regimen being the predominant therapy (32/36). Mortality varied between patients who received next line of therapy (29 out of 36 died) and those who did not receive further treatment (all 45 patients died).
- Overall, 91% of the patients died (n=74), 6% were alive and 3% were lost to follow-up during the follow-up time.
- Among those who died, PTLD and treatment-related mortality were attributed to more than 2/3 of the deaths (68%) (**Figure 1**).
- The median OS from the time of rituximab failure was 0.7 months and from PTLD diagnosis was 1.7 months. At 24 months, the estimated OS rate was less than 10% (**Figure 2**).

Figure 1. PTLD is the Most Common Reason for Death Among EBV$^+$ PTLD Patients Following HCT (n=74)

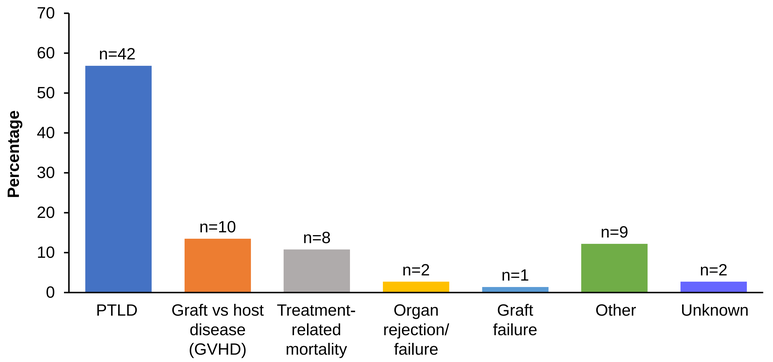
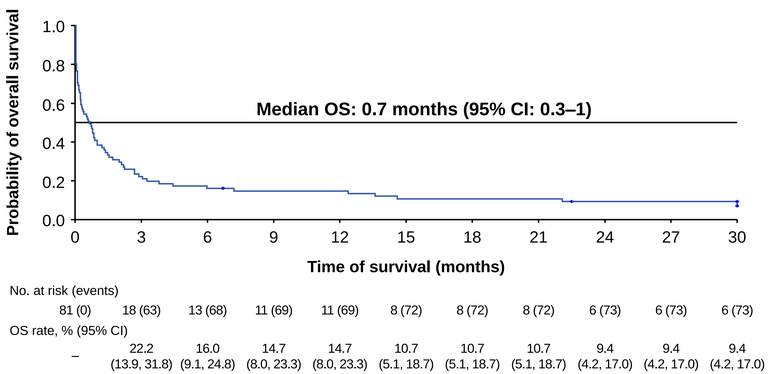


Figure 2. KM Plot for Overall Survival for EBV$^+$ PTLD Patients Post-HCT Who Failed Rituximab ± CT (n=81)



Survival was measured from the earliest date when patients became refractory or relapsed to rituximab ± CT

CONCLUSIONS

- **Evaluating the data from a large multinational, multicenter retrospective chart review of EBV$^+$ PTLD patients following HCT after failure of rituximab ± CT demonstrated poor OS with median OS of 0.7 months.**
- **A vast majority of the patients (91%) ultimately died; more than 2/3 of the deaths (68%) were related to PTLD and therapy.**
- **There remains a significant unmet need for post-HCT EBV$^+$ PTLD patients who fail rituximab ± CT.**

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