Pericardial Effusion in Patients with Chronic Lymphocytic Leukemia Treated with Bruton's Tyrosine Kinase Inhibitors

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Introduction

- Burton's tyrosine kinase inhibitors (BTKI) have revolutionized the treatment of chronic lymphocytic leukemia (CLL)
- They have a unique safety profile with rare reported life-threatening adverse events (AEs)
- Next generation BTKIs such as acalabrutinib and zanubrutinib are more specific and associated with fewer AEs.
- Pericardial effusion or tamponade (PE/T) related to BTKI treatment is an underrecognized AE with only a few cases reported to date.
- We present our institutional experience with ibrutinib-associated pericardial effusion, estimate its prevalence from a national registry, and estimate its incidence from published randomized control trials (RCTs).

Methods

1. We used two computerized databases to detect cases of PE/T in patients with CLL according to their exposure to BTKIs.
   A) An institutional database
   B) A national registry from the largest public medical organization in Israel
2. We assessed relative incidence from published RCTs where BTKI-containing regiments were compared with non-BTKI arms

Results

1) A . Institutional database

- 750 CLL patients→ 154 received BTKIs (mostly ibrutinib)→ 5 developed PE/T, 4 of whom were on ibrutinib at the time (see Table 1). one patient without therapy.
- The calculated prevalence of PE/T in CLL patients under BTKI was 2.6% (95%CI: 0.71-6.52%) with a relative risk (RR) of 15.48 (95%CI 1.74-137.5; Fisher Exact test, p-value=0.0072).

Results continued

B. National HMO registry :

- 5917 CLL → 770 treated with BTKIs→ 19 cases of PE/T: 6 after the administration of BTKI, and 13 in patients who did not receive BTKI.
- The estimated prevalence in this larger cohort was 0.78% in patients under BTKI with a RR of 3.09 (95%CI 1.18-8.1; p-value=0.029).

2) RCTs analysis:

- 7 relevant studies reported on PE/T specifically. Details are summarized in Table 2.
- Twelve cases (out of 2239 patients) of PE/T were reported analysis in the investigational arm vs 2 cases (out of 1580) in the non-BTKI containing arm.
- The calculated weighted average incidence of PE/T, according to the median exposure time on BTKI in each trial, was 216.2 cases/100,000 patient-years (PY).
- Intention to treat analysis and based on median follow up at each reported study- the incidence RR for developing PE/T in the BTKI arm was 5.91 (95%CI 4.11-8.50, p-value <0.0001) compared with the control arm, with a number needed to harm of 599 (95%CI 730-507).

Table 2. RCTs of BTKI vs CIT reporting PE/T

Study	Design	BTKi arm		Control arm		Median follow up (months)
		N. of patients	Events	N. of patients	Events	
RESONATE-2 (1)	IB vs Chl	136	1	133	0	18.4
HELIOS (2)	IB+BR vs BR+placebo	289	0	289	2	34.8
E1912 (3)	IB+R vs FCR	354	2	174	0	33.6
ALLIANCE (4)	IB+/-R vs BR	364	5	183	0	38
FLAIR (5)	IB+R vs FCR	386	1	385	0	53
SEQUOIA (6)	Zan vs BR	352	2	238	0	26.2
ELEVATE TN (7)	Acal+/-O vs Chl-O	358	2	177	0	28.3

Abbreviations: IB- ibrutinib; Chl- chlorambucil; R- rituximab; FCR- fludarabine, cyclophosphamide, rituximab; BR-bendamustine, rituximab; Zan-zanubrutinib; Acal-acalabrutinib; O-obinutuzumab

Table 1. Cases of PE/T – Institutional experience

Pt	Time from start of Ibrutinib	Dosing	AF	Treatment of tamponade	Pleural effusion drainage	Effusion type	Treatment following pericardial effusion	Predisposing event	Anticoagulation treatment/ Anti-aggregation treatment	Effusion reoccurred
1	26 months	420 mg	No	Drainage + prednisone+ colchicine	yes	Exudate Sero-bloody	Ibrutinib stopped	No	No	No
2	41 months	420 mg	Yes	Drainage + colchicine	yes	Exudate	Ibrutinib stopped for one month and then restarted	No	No	No
3	6 months	420 mg	Yes	Drainage + colchicine +NSAIDS	yes	Exudate Clear fluid	Ibrutinib stopped	No	Aspirin	No
4	1 month	420 mg	Yes	Drainage + prednisone	No	Bloody fluid	Ibrutinib stopped	URTI	No	No

Conclusions

- BTKIs are associated with an increased risk for pericardial effusion or tamponade
- Further studies are needed to appreciate its incidence in next generation BTKIs and understand the involved mechanism.

References

1.Byrd et al, NEJM 2014; 2. Chanan-Khan et al, Lancet Oncol 2016; 3. Shanafelt et al, NEJM 2019; 4. Woyach et al, NEJM 2018; 5. Hillmen et al, Lancet Oncol 2023; 6. Tam et al, Lancet Oncol 2022; 7.Sharman et al, Lancet 2020