Intestinal Lymphangiectasia with RET Tyrosine Kinase Inhibitor Therapy

AUTHORS

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ABSTRACT

Background. – As selpercatinib and pralsetinib use has gradually increased as first-line therapy for RET-altered non–small cell lung cancer (NSCLC), a growing number of adverse effects are being observed. We identified a frequent and underrecognized complication in patients treated with RET tyrosine kinase inhibitors (TKIs), intestinal lymphangiectasia (IL)

Methods. – This is a retrospective, single-center study included patients with RET-altered NSCLC treated with selective RET TKIs between 2015 and 2025. Clinicopathological features and management of patients with versus without IL were assessed.

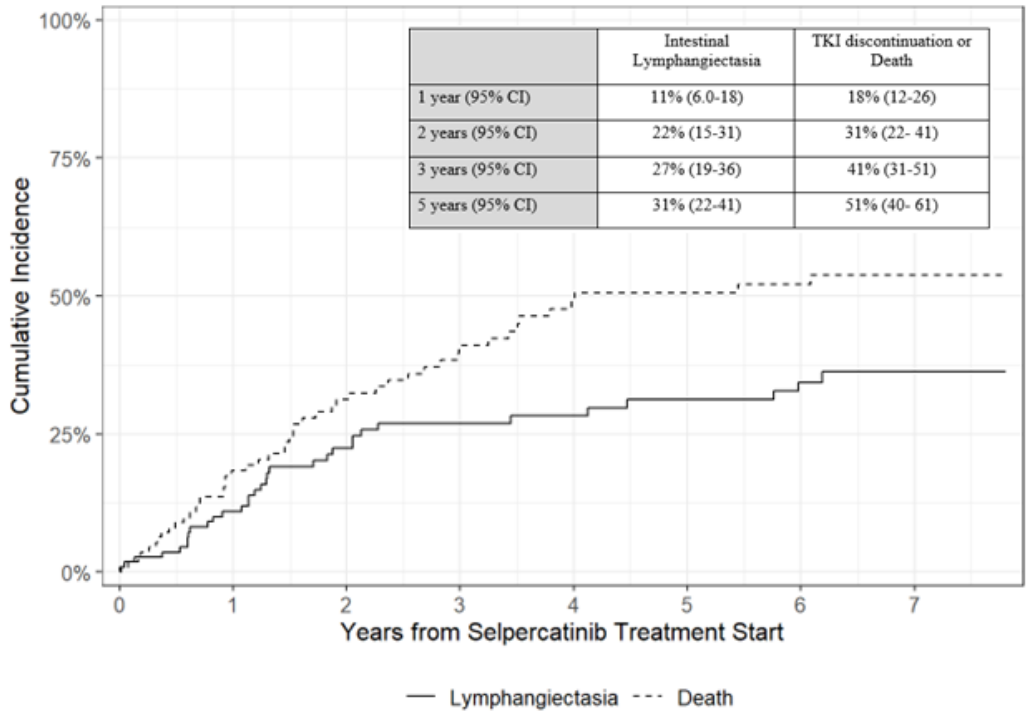
Results. - A total of 113 patients with complete clinical and radiologic follow-up were included. IL was radiologically identified in 32/110 patients treated with selpercatinib and 1/3 treated with pralsetinib (29.2% of all patients). Cumulative incidence at 1, 3, and 5 years was 11% (95% CI 6-18%), 27% (95% CI 19%-36%), and 31% (95% CI 22%-41%), respectively. Patients with IL received RET TKIs in later lines (≥3) ($p = 0.028$) more frequently than those without, but no other differences in clinical and molecular characteristics were observed. Gastrointestinal (GI) symptoms were reported in 66.6% of patients with IL. Protein loss and third-space fluid accumulation were described in 72.6% of patients and occurred more frequently in those with IL. Radiologically, the jejunum was the most affected region (90.9%), followed by the duodenum (24.2%) and the colon (18.2%). Dose reduction or temporary discontinuation of the RET TKI resulted in resolution of findings in 42.4% of cases. One patient developed fatal sepsis secondary to bacterial translocation. IL improved radiologically and/or clinically in 42% of patients post dose reduction.

Conclusion. - IL is a relatively frequent complication of RET TKI therapy, commonly associated with gastrointestinal symptoms and protein loss, highlighting the importance of early detection and individualized management.

Keywords. – Intestinal Lymphangiectasia: RET tyrosine kinase inhibitor; Selpercatinib; Pralsetinib; Non–Small Cell Lung Cancer; Protein-Losing Enteropathy

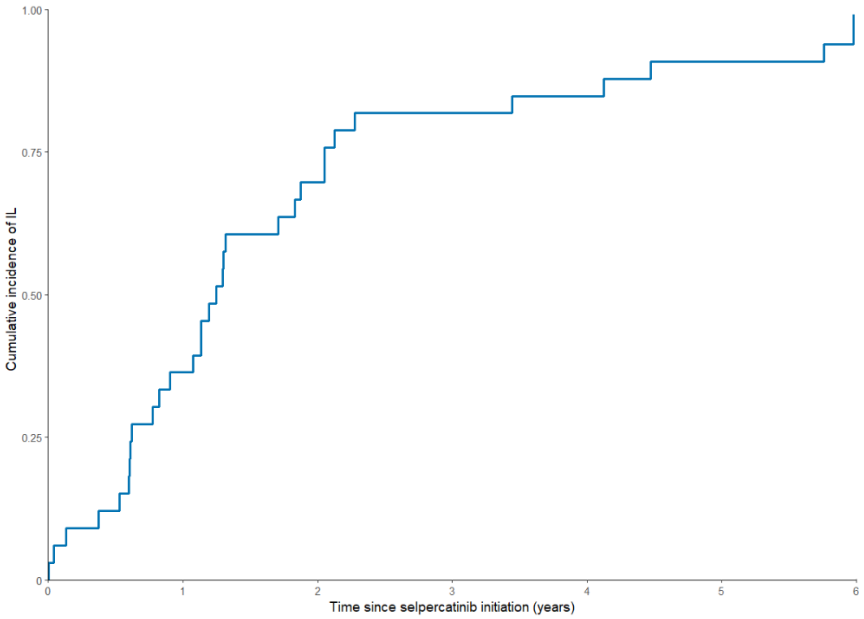
FIGURES

A.



	Intestinal Lymphangiectasia	TKI discontinuation or Death
1 year (95% CI)	11% (6.0-18)	18% (12-26)
2 years (95% CI)	22% (15-31)	31% (22- 41)
3 years (95% CI)	27% (19-36)	41% (31-51)
5 years (95% CI)	31% (22-41)	51% (40- 61)

B.



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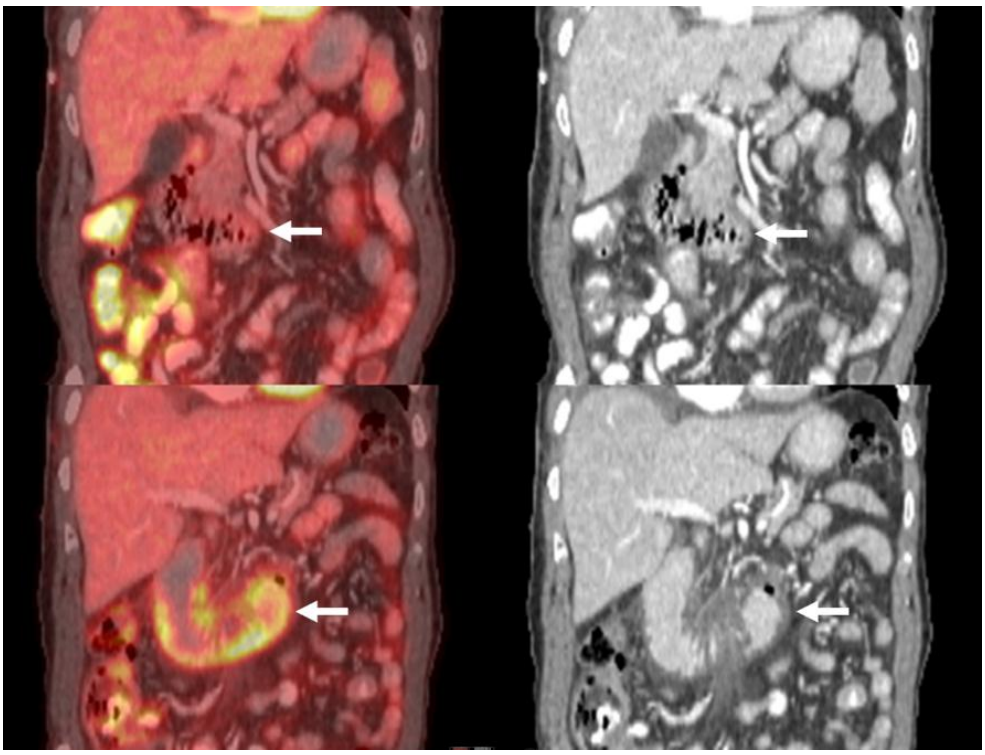

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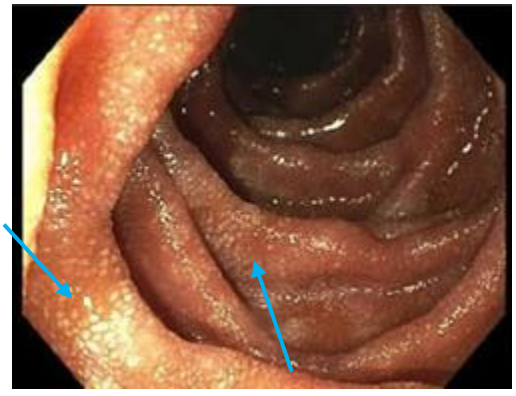

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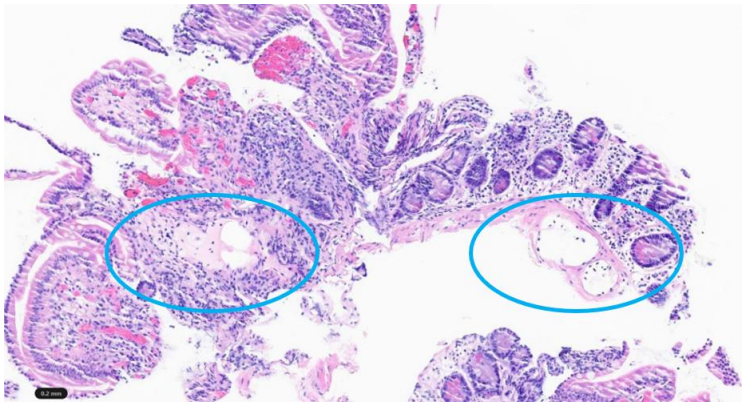

Figure 1. Intestinal Lymphangiectasia (IL) Acquisition and Characteristics.

(A) A competing risk analysis was performed for IL acquisition in our cohort. Patients with and without IL of our final series were included (N=113 patients). The event of

interest was the occurrence of IL while the competing event was death or discontinuation of RET TKI therapy.

(B) Time to onset of IL after RET TKI therapy.

(C) Pre and post-RET TKI imaging of the duodenum (normal (top) and then with FDG avid lymphangiectasia (bottom)).

(D) Endoscopic findings in a patient with IL showing mild whitish villous appearance.

(E) Histologic changes in an IL sample with mild dilation of mucosal or submucosal lymphatics (highlighted with blue circles).

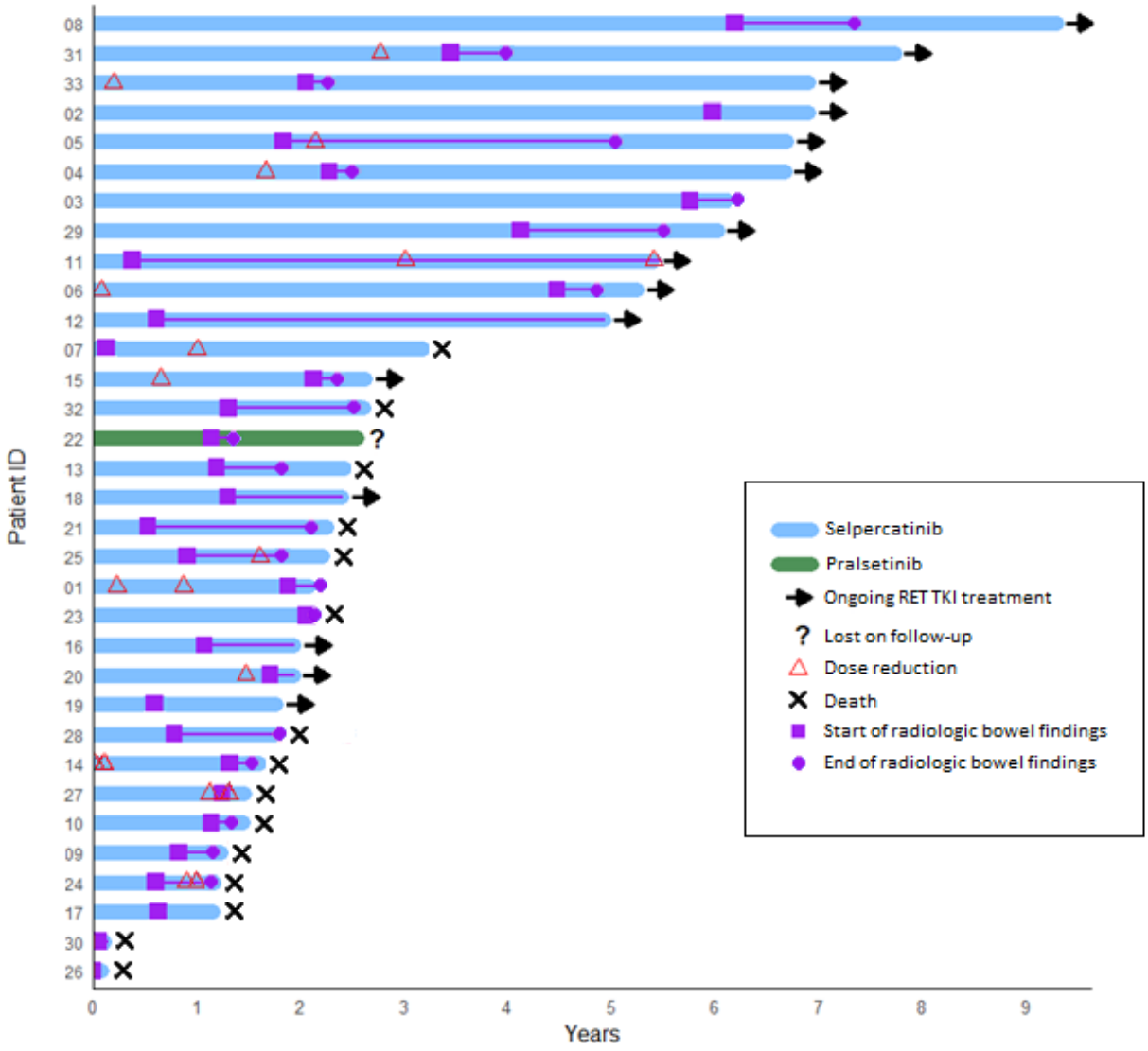

Figure 2. Patient Course and Management. Clinical course of patients diagnosed with radiological findings suggesting probable intestinal lymphangiectasia (N=33). Time 0 represents the initiation of the first RET tyrosine kinase inhibitor.

	Overall (N=113)	With IL (N=33)	Without IL (N=80)
Sex, N (%)			
Female	63 (56)	20 (61)	43 (54)
Male	50 (44)	13 (39)	37 (46)
Age at Stage IV diagnosis, years (IQR)	62 (54-67)	64 (52-68)	62 (55-66)

Smoking Status, N (%)			
Never	76 (67)	25 (76)	51 (64)
Former/smoker	37 (33)	8 (24)	29 (36)
Histology, N (%)			
Adenocarcinoma	103 (91)	32 (97)	71 (89)
Large Cell Neuroendocrine carcinoma	8 (7)	1 (3)	7 (9)
Others	2 (2)	0 (0)	2 (3)
Race, N (%)			
White	86 (76)	28 (85)	58 (73)
Asian-Far East/Indian Subcont	19 (17)	3 (9)	16 (20)
Black or African American	8 (7)	2 (6)	6 (8)
Genetic alteration, N (%)			
Fusion	110 (97)	33 (100)	77 (96)
Mutation	3 (3)	0 (0)	3 (4)
Subtype			
KIF5B-RET	74 (65)	52 (65)	22 (67)
CCDC6-RET	24 (21)	19 (24)	5 (15)
NCOA4-RET	3 (3)	3 (4)	0 (0)
ERC1-RET	2 (2)	2 (3)	0 (0)
M918T	2 (2)	2 (3)	0 (0)
Other*	8 (7)	2 (3)	6 (18)
PD-L1 level expression			
<1%	44 (39)	15 (45)	29 (36)
1-49%	27 (24)	5 (15)	22 (28)
≥ 50%	27 (24)	10 (30)	17 (21)
Unknown	15 (13)	3 (9)	12 (15)
Line Received RET TKI, N (%)			
1st line	54 (48)	11 (33)	43 (54)
2nd line	36 (32)	10 (30)	26 (33)
3rd line	10 (9)	4 (12)	6 (8)
≥4th line	13 (12)	8 (14)	5 (6)

Table 1. Main characteristics of patients treated with a RET tyrosine kinase inhibitor. and of patients who developed intestinal lymphangiectasia (IL) versus those who did not. IQR, interquartile range; TKI, tyrosine kinase inhibitor.

*“Other” includes *CLIP1, EML4, ERCC6, GRIPAP1, KIAA1468* and *RBPMS* fusions and C634R mutation.