

Predictive value of weight and BSA in assessing toxicity during ALK tyrosine kinase inhibitors in non-small cell lung cancer

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Background

ALK tyrosine kinase inhibitors (ALK TKi) are an essential treatment with excellent results in survival and QoL. Unlike chemotherapy, ALK-TKIs are started at a standard dose regardless of patients' weight and body surface area (BSA). To explore whether body size variables might affect toxicity and efficacy, we undertook this retrospective analysis to determine the influence of weight and BSA on treatment toxicity, need for dose adjustment and outcomes.

Methods

Clinic-demographic variables, ALK-TKIs, toxicity and outcomes were collected from electronic medical charts. Weight and BSA at treatment initiation for each ALK-TKi were divided into quartiles (Q1-Q4) for descriptive analysis. Associations between BSA, weight, and dose modification (DM), temporary interruption (TI), and permanent discontinuation (PD) due to toxicity were assessed using generalized linear mixed modelling. Relationships between BSA, weight, and survival were assessed using Kaplan-Meier curves and log-rank tests.

Results

Baseline characteristics of the 147 ALK-positive NSCLC patients seen between July 2012- March 2024, are summarized in **Table 1**. There were differences in BSA between sex and ethnicity, with more males in the highest BSA Q4 (14% vs 86%, $p<0.001$), and more females (92% vs 8%, $p<0.001$) and Asians in the lowest BSA Q1 (81% vs 8% Caucasian, $p<0.001$).

Higher weight at start of ALK-TKi was associated with significant increase in frequency for dose reductions (DR) at any time, (aOR= 1.18 $p=0.039$), as was BSA (aOR 1.80, $p=0.048$). More treatment discontinuation (TD) was associated with higher weight and BSA for TI (weight aOR 1.23, $p=0.007$, and BSA aOR=2.15, $p=0.008$); and non-significant trends for PD (weight aOR=1.24, $p=0.12$, and BSA aOR=2.28, $p=0.11$) (**Table 3**).

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Results

Table 1. Baseline Characteristics

Variables	n=147 (%)
Age	58.1 (30.5 – 92.7)
Sex	
Female	80 (55)
Male	66 (45)
Ethnicity	
Asian	73 (50)
Caucasian	54 (37)
Other	13 (9)
Unknown	7 (5)
Smoking status	
Ever smoker	29 (20)
Never smoker	115 (79)
Unknown	2 (1)
Histology	
Adenocarcinoma	138 (95)
Squamous	2 (1)
Other	6 (4)
TP53	
Mutated	9 (6)
Wild Type	39 (27)
Unknown	98 (67)
Line of ALK-TKi*	
Crizotinib	
1 st line	56
2 nd line	3
Ceritinib	
1 st line	9
2 nd line	21
Alectinib	
1 st line	65
2 nd line	42
Brigatinib	
1 st line	8
2 nd line	25
Lorlatinib	
1 st line	9
2 nd line	35

Table 2. Correlation between dose modification based on BSA and each ALK- TKi

Treatment	Dose modification	Overall	Q1 <1.59 (n=37)	Q2 (1.59-1.73) (n=36)	Q3 (1.74-1.89) (n=37)	Q4 (≥1.90) (n=37)
Crizotinib ≥1 Line (n=59)	None	22	6	7	5	4
	Any dose reduction	7	3	0	2	2
	Any temporary discontinuation	24	6	9	5	4
	Any permanent discontinuation due to toxicity	6	0	2	2	2
Ceritinib ≥1 Line (n=26)	None	15	4	3	4	4
	Any dose reduction	0	0	0	0	0
	Any temporary discontinuation	9	1	3	4	1
	Any permanent discontinuation due to toxicity	2	1	0	0	1
Alectinib ≥1 Line (n=104)	None	48	16	9	11	12
	Any dose reduction	21	5	5	8	3
	Any temporary discontinuation	28	4	9	5	10
	Any permanent discontinuation due to toxicity	7	3	2	0	2
Brigatinib ≥1 Line (n=33)	None	15	3	5	2	5
	Any dose reduction	3	1	1	1	0
	Any temporary discontinuation	9	3	1	2	3
	Any permanent discontinuation due to toxicity	6	1	0	3	2
Lorlatinib ≥1 Line (n=41)	None	23	3	7	8	5
	Any dose reduction	4	2	0	0	2
	Any temporary discontinuation	13	3	3	2	5
	Any permanent discontinuation due to toxicity	1	0	1	0	0

p values (Fisher exact test) >0.05

Figure 1. Survival outcomes in relation to weight and BSA. **A.** Overall Survival to 10 years, by BSA quartile; **B.** Overall Survival to 10 years, by weight quartile; **C.** Progression free survival to 10 years, by BSA quartile; **D.** Progression free survival to 10 years, by weight quartile

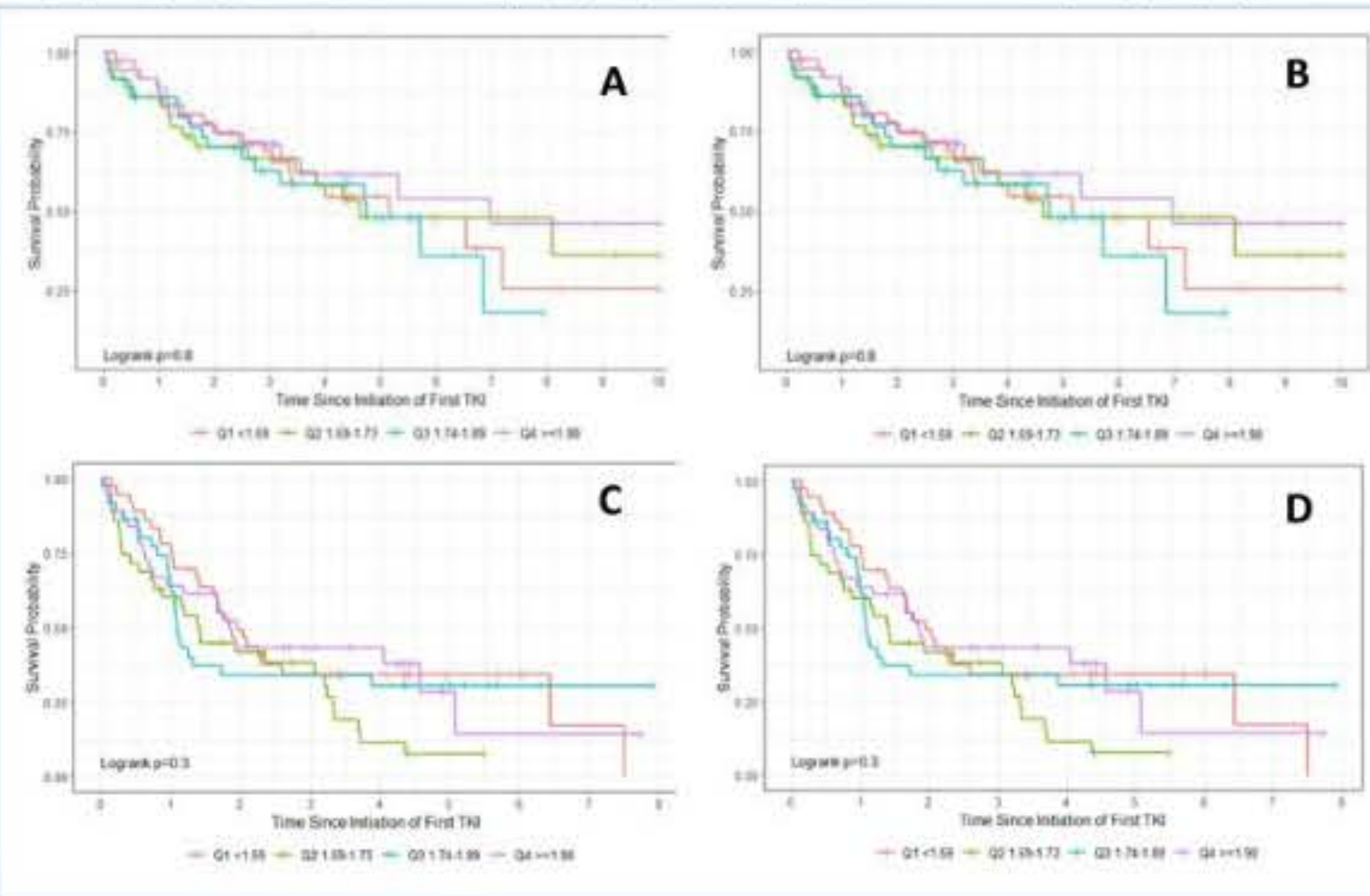


Table 3. Risk for dose modification based on weight/BSA

Independent variable	Dependent variable	Risk	#Individual patients /Observation
BSA per 0.5-unit increase	Dose reduction	OR=1.80, 95%IC 1.00-3.21 $p=0.048$	147/291
Weight per 10 kg increase	Dose reduction	OR=1.18, 95% IC 1.01-1.38 $p=0.039$	147/291
BSA per 0.5-unit increase	Temporary interruption	OR=2.15, 95% IC 1.22-3.78 $p=0.008$	139/279
Weight per 10 kg increase	Temporary interruption	OR=1.23, 95% IC 1.06-1.44, $p=0.007$	139/279
BSA per 0.5-unit increase	Permanent discontinuation	OR 2.28, 95% IC 0.83-6.27, $p=0.11$	139/279
Weight per 10 kg increase	Permanent discontinuation	OR=1.24, 95% IC 0.95-1.62, $p=0.12$	139/279

Lower dose intensity (DI) during TKi therapy (0-100% of total dose), was associated with higher weight ($p<0.018$) and higher BSA ($p<0.008$). There was no correlation between DR or TD based on the line or individual ALK-TKi administered (**Table 2**). Interestingly, in the adjusted analysis, age and sex also were associated with DR, DI, TI and PD only for age.

Despite differences in the need for DM, weight and BSA were not negatively associated with progression-free survival ($p=0.3$) or overall survival ($p=0.8$) (**Figure 1**).

Conclusions

Lower weight and BSA did not predict for increased toxicity leading to dose reduction and temporary or permanent discontinuation on ALK-TKIs. Moreover, differences in weight and BSA did not negatively impact treatment outcomes.

References

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