

Induction ALK-TKIs for stage III non-small cell lung cancer harboring ALK fusion: A single-center experience with 3-year follow-up

Objective

This study aims to evaluate clinical efficacy and safety of induction ALK-TKIs in stage III non-small cell lung cancer (NSCLC) harboring ALK-fusion.

Methods

Consecutive data from single center were retrospectively collected and those who were pathologically confirmed stage IIIA-IIIB treated with induction ALK-TKIs initially were eligible for subsequent analysis. Response assessment, surgical outcome as well as survival were fully reviewed. Longitudinal single-cell RNA sequencing from two patients treated with Alectinib who happened to exhibit polarized pathological response were analyzed.

Results

39 patients treated with either Alectinib or Crizotinib initially were consecutively collected. 29 patients received surgery after induction ALK-TKIs with median treatment duration of 95 days while others received radiotherapy or continued TKIs treatment. Among those who had surgery, all patients had R0 resection without postoperative radiotherapy. Median operative duration, length of stay and intraoperative blood loss was 150mins, 5 days and 40ml, respectively. No significant difference was found between groups. Only two patients suffered grade 2 postoperative complication in regard to Clavien-Dindo score. 10.3% (3/29) patients had conversion to thoracotomy during minimally invasive lobectomy. No 30-day or 90-day mortality was observed. Induction Alectinib showed numerically superior pathological response compared to Crizotinib with both major pathological response (MPR) (9/16, 56.3% vs. 4/13, 30.8%, $p=0.26$) and complete pathological response (pCR) (6/16, 37.5% vs. 2/13, 15.4%, $p=0.24$). Upon a median follow-up time of 35.2 months, patients received induction Alectinib had significantly longer PFS (not reach (NR) vs. 17.9 months, $p=0.002$) and numerically improved OS (NR vs. 62.6, $p=0.226$) compared to Crizotinib. Longitudinal single-cell RNA sequencing from two patients revealed increased tumor stemness and induced more suppressive immune microenvironment defined as increased PDCD1, TIGIT, and CTLA4 expression in excessive residual tumor while highly inflamed microenvironment defined by high GNLY, CX3CR1 and CD48 expression along with relatively low infiltrating Treg and Tex in resected specimen which achieved pCR.

Conclusions

Induction ALK-TKIs could be clinically feasible in stage III NSCLC without influencing radical surgery. Alectinib as induction setting continues to show superior efficacy and long-term benefit compared to Crizotinib.

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Characteristic	Overall N=39	Alectinib	Crizotinib	p-value	methods
		N=20	N=19		
Age, mean \pm SD	48.6 \pm 10.2	50.7 \pm 10.1	46.47 \pm 10.4	0.206	T test
Gender, n (%)				1.000	Fisher.test
Female	18 (46.2%)	9 (45.0%)	9 (47.4%)		
Male	21 (53.8%)	11 (55.0%)	10 (52.6%)		
Smoking, n (%)				0.716	Fisher.test
Never-smoker	30 (76.9%)	16 (80.0%)	14 (73.7%)		
Ever-smoker	9 (23.1%)	4 (20.0%)	5 (26.3%)		
Stage, n (%)				0.200	Fisher.test
IIIA	16 (41.0%)	6 (30.0%)	10 (52.6%)		
IIIB	23 (59.0%)	14 (70.0%)	9 (47.4%)		
Radiological response, n (%)				1.000	Fisher.test
PR	29 (74.4%)	15 (75.0%)	14 (73.7%)		
SD	10 (25.6%)	5 (25.0%)	5 (26.3%)		
Local treatment, n (%)				0.124	Chisq.test
Lobectomy	24 (61.5%)	12 (60.0%)	12 (63.1%)		
Pneumonectomy	1 (2.5%)	0 (0.0%)	1 (5.3%)		
RT	4 (10.3%)	3 (15.0%)	1 (5.3%)		
Segmentectomy	1 (2.5%)	1 (5.0%)	0 (0.0%)		
Wedge	3 (7.7%)	3 (15.0%)	0 (0.0%)		
Continue TKIs	6 (15.5%)	1 (5.0%)	5 (26.3%)		
Pathological response, n (%)				0.283	Fisher.test
non-MPR*	26 (66.7%)	11 (55.0%)	15 (79.0%)		
MPR	5 (12.8%)	3 (15.0%)	2 (10.5%)		
pCR	8 (20.5%)	6 (30.0%)	2 (10.5%)		
Treatment duration, median (IQR) [#]	95 (80, 145)	102 (90, 165)	81.5 (59.25, 96.5)	0.036	Wilcoxon

*Those who did not receive surgery and comprehensive pathological evaluation were counted as non-MPR. [#]Those who continue TKIs treatment were excluded.