Impact of pre-treatment AXL expression on osimertinib efficacy in patients with non-small cell lung cancer with *EGFR* mutation

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Abstract

Background: A novel EGFR-tyrosine kinase inhibitor (TKI) osimertinib has marked efficacy in patients with EGFR-mutated non-small cell lung cancer (NSCLC). However, some patients show the intrinsic resistance and an insufficient response to Osimertinib. Increased expression of the anexelekto (AXL) protein in tumors is reported to be associated with poor prognosis in patients with several types of cancer. We previously reported the crucial role of the AXL pathway in the intrinsic resistance to EGFR-TKIs in *EGFR*-mutated NSCLC cells. Moreover, AXL overexpression in *EGFR*-mutated NSCLC specimens was negatively associated with the therapeutic efficacy of first- and second-generation EGFR-TKIs. However, the relationship between AXL expression in tumors and the therapeutic efficacy of Osimertinib is still unclear.
Methods: We retrospectively enrolled 30 patients with advanced or relapsed NSCLC with *EGFR*-activating mutations from four institutions in Japan. All patients were administered Osimertinib as the first-line treatment between August 2017 and March 2019.
Results: Twenty-two (73.3%) patients were female; 21 (70.0%) patients had never smoked. The median age of patients was 71.0 years (range, 44–88 years of age). The EGFR-activating mutations were deletion in exon 19 in 16 (53.3%) patients; L858R missense mutation in exon 21 in 12 (40.0%) patients; and other types in 2 (6.6%) patients. High (3+), intermediate (2+), low (1+), and no (0) pre-treatment expression of AXL in tumors were observed in 2 (6.7%), 4 (13.3%), 12 (40.0%), and 12 (40.0%) patients, respectively. The maximal tumor shrinkage rate following osimertinib treatment in the patients with AXL expression scores of 0 and 1+ was higher than that in patients with AXL expression scores of 2+ and 3+ (44.12% vs. 25.93%, p = 0.094).
Conclusions: Pre-treatment AXL expression in tumors might be a promising predictor for osimertinib treatment in patients with *EGFR*-mutated NSCLC.

Background

- Current phase III clinical trials demonstrated that the treatment with osimertinib showed better outcomes than that of first-generation EGFR-TKIs at the first line setting for advanced EGFR-mutated NSCLC patients. However, approximately 20% of EGFR-mutated NSCLC patients show intrinsic resistance to osimertinib *(N Engl J Med 2018;378:113–25)*.
- Anexelekto (AXL) is a tyrosine kinase receptor belonging to the TAM family of proteins. The activation of AXL signaling in tumors is associated with acquired resistance to several targeted molecular therapy drugs and chemotherapeutic *agents (Nat Rev Cancer 2014;14: 769–85).*
- We previously revealed the role of the AXL pathway in the intrinsic resistance to osimertinib and the emergence of osimertinib-tolerant cells in EGFR-mutated NSCLC cells *(Nat Commun 2019;10:259).*

Research aim

To elucidate the relationship between AXL expression in tumors and the therapeutic efficacy of osimertinib in patients with EGFR mutated NSCLC.

Results

Table 1. Patient characteristics (N = 30)

Characteristics		N (%)
Age: Median [range]		71.5 [44.0 - 88.0]
Age	<70 years	13 (43.3)
	>=70 years	17 (56.7)
Sex	Male	8 (26.7)
	Female	22 (73.3)
Smoking status	Never smoker	21 (70.0)
	Current or former smoker	9 (30.0)
Clinical stage	IV	24 (80.0)
	postoperative relapse	6 (20.0)
Histology	Non-squamous cell carcinoma	29 (96.7)
	Squamous cell carcinoma	1 (3.3)
EGFR mutation	Del19	16 (53.3)
	L858R	12 (40.0)
	Others	2 (6.7)
AXL expression	0	12 (40.0)
	1+	12 (40.0)
	2+	5 (16.7)
	3+	1 (3.3)
Response to treatmet	PR	20 (66.7)
	SD	10 (33.3)
	Response rate	66.67%
	Disease control rate	100.00%

Table 2. Patients characteristics according to AXL expression in tumors

Characteristics		AXL expression 0, +1, N = 24	AXL expression 2+, 3+,N = 6	p value
Age: Median [range]		71.5 [44.0 - 88.0]	71.0 [65.0 - 78.0]	1
Age	<70 years	10 (41.7)	3 (50.0)	1
	>=70 years	14 (58.3)	3 (50.0)	
Sex	Male	6 (25.0)	2 (33.3)	0.645
	Female	18 (75.0)	4 (66.7)	
Smoking status	Never smoker	16 (66.7)	5 (83.3)	0.637
	Current or former smoker	8 (33.3)	1 (16.7)	
Clinical stage	IV	18 (75.0)	6 (100.0)	0.302
	postoperative relapse	6 (25.0)	0 (0.0)	
Histology	Non-squamous cell carcinoma	23 (95.8)	6 (100.0)	1
	Squamous cell carcinoma	1 (4.2)	0 (0.0)	
EGFR mutation	Del19	12 (50.0)	4 (66.7)	0.793
	L858R	10 (41.7)	2 (33.3)	
	Others	2 (8.3)	0 (0.0)	
Response to treatmet	PR	17 (70.8)	3 (50.0)	0.372
	SD	7 (29.2)	3 (50.0)	
	Response rate	70.83%	50.00%	0.372
	Disease control rate	100.00%	100.00%	1

Results

Figure 1. immunohistochemistry for AXL using tumor specimens

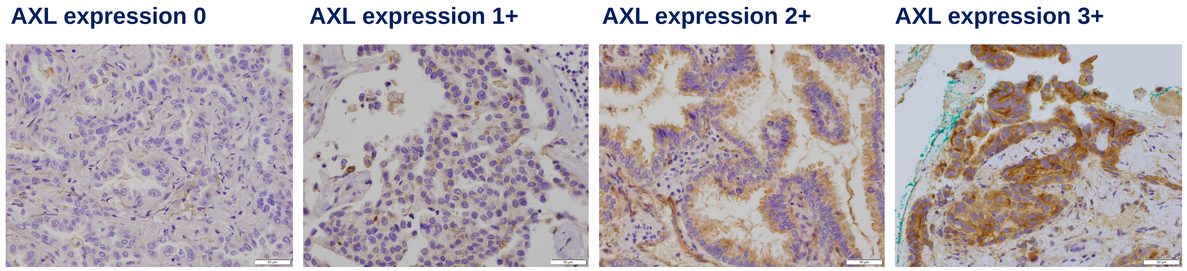

Figure1. Since immunohistochemical studies have shown that AXL is present primarily in the cytoplasm of cells and that its staining varies in intensity, we quantified its expression as negative (0), weak (1+), moderate (2+), and strong (3+) compared to vascular endothelial cells as an internal control.

Figure 2. Response rate of osimertinib according to AXL expression in tumors

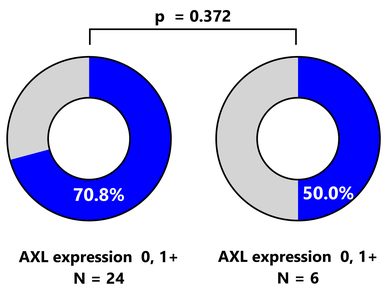

Figure 2: Osimertinib tended to be more effective in patients with AXL low in tumors compared to patients with AXL high in tumors (Response rate: 70.8% vs. 50.0%).

Figure 3. Kaplan-Meier curve for PFS and OS according to AXL expression in tumors

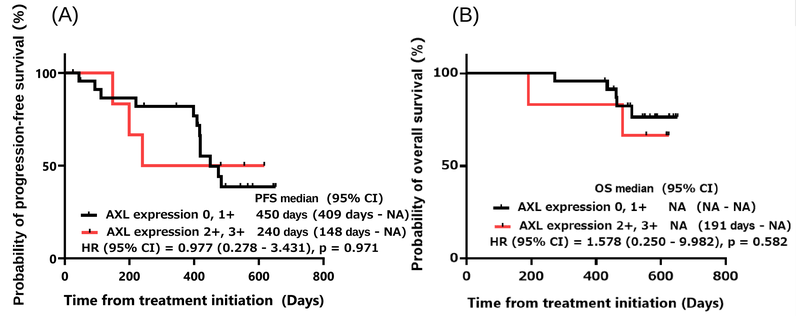

Figure 3: (A) Patients with AXL low in tumors tended to have longer PFS compared to patients with AXL high in tumors (HR: 0.977, 95% CI: 0.278–3.431, P = 0.971). (B) AXL low group tended to have longer OS relative to the AXL high group (HR: 1.578, 95% CI: 0.250–9.982, P = 0.582).

Conclusion

Pre-treatment AXL expression in tumors might be a promising predictor for osimertinib treatment in patients with *EGFR*-mutated NSCLC. Therefore, further large-scale studies are warranted to validate the relationship between pre-treatment AXL expression in tumors and the efficacy of osimertinib.