The usefulness of liquid biopsy for ctDNA in patients with EGFR-mutant NSCLC during and after treatment with EGFR-TKIs

Takuma Yokoyama[1], Go Naka[2], Hiroo Ishida[3], Kazuma Kishi[4], Yasuo Ohashi[5], Hideo Kunitoh[6]

[1]Kyorin University Hospital, Tokyo/Japan, [2]National Center for Global Health and Medicine, Tokyo/Japan, [3]Showa University School of Medicine, Tokyo/Japan, [4]Toranomon Hospital, Tokyo/Japan, [5]Chuo University, Tokyo/Japan, [6]Japanese Red Cross Medical Center, Tokyo/Japan

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Comprehensive Support Project

Background 1

- Treatment with 1st or 2nd generation EGFR-TKIs is effective for NSCLC patients harboring EGFR mutation. However, acquired resistance is inevitable after a median period of 9 to 14 months.
- Although the resistance mechanisms vary, the most common one is T790M second mutation, which accounts for approximately 60% [1].
- Osimertinib, a 3rd generation EGFR-TKI targeting EGFR T790M mutation, is reported to be highly active against T790M positive NSCLC[2] and has been approved in Japan, as well as in the United States and Europe. Its efficacy is low in T790M-negative tumors which got acquired resistance to 1st or 2nd generation EGFR-TKIs.
- To detect T790M mutation following acquired resistance, re-biopsy of the tumor is necessary.
- However, re-biopsy is often difficult and risky, depending on the size or location of the tumor. There is also a possibility of false-negative due to intra-tumor heterogeneity.

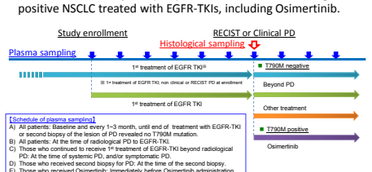
Background 2

- The optimal timing of treatment change remains elusive for an "effective" TKI. Many patients could receive benefit from "beyond-PD" TKI, and minor radiological worsening may not be the best time for histological exploration, including search for T790M. T790M may be evident, if ever, only after overt worsening (clinical PD) of the disease.
- Frequent re-biopsies via invasive procedures (bronchoscopy or needle biopsy) are infeasible in the usual care of NSCLC patients.
- Circulating tumor DNA (ctDNA) detected in the plasma sample is recognized as a noninvasive biomarker for quantifying the molecular analysis of NSCLC.
- Recently, Cobas EGFR Mutation Test® has been approved in Japan, using plasma specimens as a companion diagnostic test for the detection of EGFR mutations to identify such patients with NSCLC; however, its clinical utility in the trajectories of the patients is yet to be established.
- Cobas EGFR Mutation Test® is a noninvasive test, but its clinical data, including detection rate of T790M and the optimal timing of re-biopsy, are not sufficient.
- T790M monitoring in patients receiving Osimertinib by plasma ctDNA could give valuable clinical information.

Study design and purpose

Study Design

- Multicenter, prospective cohort study in Japan.
- To investigate the diagnostic value of plasma ctDNA of EGFR mutations in the trajectory of patients with EGFR activating mutation-positive NSCLC treated with EGFR-TKIs, including Osimertinib.



Study design and purpose

Sample size justification

In the prior CSPOR-LC02 study (Observational study of treatment of EGFR mutation positive advanced or recurrent NSCLC: UMIN000010538), radiological PD was documented in approximately 80% of the patients. In the 80% of the patients who acquired resistance to gefitinib, about 60% patients are presumed to have T790M.
From the above results, this study uses descriptive statistics, and it was set to 120 cases in consideration of feasibility of research.

Primary endpoint

- The plasma DNA T790M positivity rates by Cobas EGFR Mutation Test® in the T790M positive tumors patients.
- The plasma DNA T790M positivity rates by Cobas EGFR Mutation Test® at each clinical point.

Secondary endpoints

- The plasma DNA EGFR Exon 19 deletion or Exon 21 L858 mutation positivity rates by Cobas EGFR Mutation Test® in clinical courses.
- Time from plasma T790 positivity to tissue T790M positivity in the tissue T790M-positive cases.
- Response Rate and PFS with Osimertinib.
- Response Rate and PFS with re-challenge of other EGFR-TKIs.

Eligibility Criteria

Key inclusion criteria

1. Histologically confirmed advanced or postoperative recurrent NSCLC harbouring activating EGFR mutation.
[Definitions of activating EGFR mutation]
   A) Exon 19 deletion (regardless of subtype)
   B) Exon 21 L858R
   C) Other rare mutations (e.g. Exon 18 G719X)
   * De novo T790M not excluded.
2. Being treated with an EGFR-TKI without disease progression, or, To be treated with an EGFR-TKI.
3. ECOG PS 0-2.
4. Age ≥ 20 years
5. Signed informed consent.

Key exclusion criteria

1. Prior therapy with an EGFR-TKI (other than the current therapy, if being treated with one)

Data Set

Enrollment

Between September 30, 2016, and March 10, 2017, at 15 centres in Japan.

- Enrollment: 122 patients
- Ineligible: 1 patient (prior EGFR-TKI therapy)
- Eligible and assessable: 121 patients

Data cut-off for this analysis: August 31, 2017

- Collected CRF of 6 months after enrollment: 67 patients
- Not reached 6 months after enrollment: 54 patients
- Total 803 plasma samples between September 30, 2016, and September 12, 2017

Patient characteristics

Characteristics	No. of patients (n = 121)	%
Gender (Male/Female)	42/79	34.7/65.3
Age median (range)	72 (40-92)	
ECOG PS 0/1/2	64/54/3	52.9/44.6/2.5
Smoking history Never/Current/Past/ unknown	80/3/36/2	66.1/2.5/29.8/1.7
Clinical stage IIIA/IIIB/IV/Recurrence	1/3/78/39	
Recurrence Postoperative/irradiation /postoperative and radical irradiation	36/2/1	92.3/5.1/2.6
EGFR mutation		
Ex19 Del	61	50.4
Ex21 L858R	55	45.5
Other	5	4.1
T790M Denovo	0	0
EGFR samples		
Lung	93	76.9
Mediastinal Hilar lymph	6	5.0
Other lymph	3	2.5
Pleural effusion	15	12.4
Other	4	3.3

The Metastatic lesion before the therapy of EGFR-TKI		
Brain	33	15.5%
Meningeal dissemination	2	0.9%
Bone	32	15.0%
Liver	8	3.8%
adrenal gland	4	1.9%
Lung	56	26.3%
Pleural dissemination	32	15.0%
Malignant pleural effusion	29	13.6%
Pericardial effusion	2	0.9%
Other	15	7.0%
Total	213	100.0%

History of treatment at enrollment

Radiation irradiation site at enrollment	n	(%)
Brain	10	55.6%
Bone	3	16.7%
Chest (primary)	1	5.6%
Chest(metastases)	1	5.6%
Other	0	0.0%
Brain, bone	2	11.1%
Bone, others	1	5.6%
Total	18	100.0%

History of Cytotoxic agent	n	(%)
1 regimen	18	85.7%
2 regimens	2	9.5%
3 regimens	1	4.8%
Total	21	100.0%

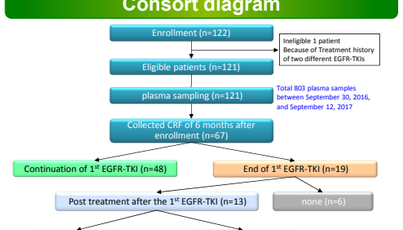
1st EGFR-TKI at enrollment

Status of EGFR-TKI at enrollment	n	(%)
Using before registration	103	85.1%
Using after registration	18	14.9%
Total	121	100.0%

Treatment with 1st EGFR-TKI	n	(%)
Gefitinib	50	41.3%
Erlotinib	40	33.1%
Afatinib	31	25.6%
Total	121	100.0%

Best overall tumor Response of 1st EGFR-TKI at enrollment	n	%
CR	10	9.7%
PR	71	68.9%
SD	12	11.7%
NE	10	9.7%
Total	103	100.0%

Consort diagram



Results

Best overall tumor Response of 1st EGFR-TKI	n	%
CR	8	11.9%
PR	39	58.2%
SD	10	14.9%
PD	8	11.9%
NE	2	3.0%
Total	67	100.0%

Treatment status of 6 months after enrollment	n	%
Continuation of 1st EGFR-TKI	48	71.6%
End of 1st EGFR-TKI	19	28.4%
Total	67	100.0%

Post treatment after the 1st EGFR-TKI	n	%
Osimertinib	4	21.1%
EGFR-TKI (other Osimertinib)	3	15.8%
EGFR-TKI+Bevacizumab	1	5.3%
Platinum regimen	5	26.3%
None	6	31.5%
Total	19	100.0%

1st Re-biopsy (histological samples)	n	%
Yes	10	14.9%
No	57	85.1%
Total	67	100.0%

The lesion of 1st Re-biopsy (histological samples)	n	%
Lung	6	60.0%
Mediastinal Hilar lymph	1	10.0%
Pleural effusion	2	20.0%
Other	1	10.0%
Total	10	100.0%

Detection of EGFR mutation by 1st Re-biopsy (histological samples)	n	%
Positive		
Only common mt	4	40.0%
Common mt+T790M※	2	20.0%
Negative	4	40.0%
Total	10	100.0%

※ No detection of T790 in plasma samples

The treatment after detection of T790M by histological samples	N	%
Osimertinib	1	50.0%
Beyond PD	1	50.0%
Total	2	100.0%

Detection of T790M after 1st EGFR-TKI treatment by plasma samples	n	%
Positive	11※	9.1%
Negative	110	90.9%
Total	120	100.0%

※ No detection of T790 by histological samples

The treatment after Detection of T790M by plasma samples	n	%
Osimertinib	3	27.3%
Beyond PD	2	18.2%
unknown	6	54.5%
Total	11	100.0%

Conclusions

- In this multi-institutional study, periodic monitoring of ctDNA for EGFR mutation, including T790M, was feasible, with 121 patients. So far, 803 plasma specimens were collected in 11 months for analysis of EGFR gene mutations.
- So far, 19 patients got acquired resistance to the initial EGFR-TKI. Of those, ctDNA revealed T790M in 11 patients, whereas histological re-biopsy revealed T790M in 2 patients.
- Follow-up of the patients and accumulation of the data would reveal value of T790M ctDNA monitoring in EGFR-TKI-treated patients, including those receiving osimertinib.

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  - Showa University Fujigaoka Hospital
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