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Targeted Therapy Followed by Cytotoxic Chemotherapy in Preoperative Patients With Locally Advanced Lung Adenocarcinoma

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Abstract. *Background: Although oncogene-targeted therapy is a first-line treatment for advanced, unresectable lung adenocarcinoma harboring a target gene mutation, its effect on potentially resectable, locally advanced lung adenocarcinoma remains unclear. Patients and Methods: Ten patients with clinically diagnosed stage III lung adenocarcinoma harboring a target gene mutation were enrolled in the current feasibility study of targeted therapy followed by cytotoxic chemotherapy (platinum and pemetrexed) before radical surgery. Results: Complete resection was accomplished in all nine patients who went on to surgery (one patient refused surgery), and all of these patients recovered without major postoperative complications. Overall, almost all of the patients who underwent surgery remain disease-free after a median follow-up of 22 months since the initial treatment, with only one patient dying of recurrence. Conclusion: Radical surgery after the sequential use of cytostatic and cytotoxic drugs resulted in a favorable short-term outcome.*

Surgical resection remains a potentially curative option for locoregional non-small-cell lung cancer. However, according to previous phase III trials, multimodality treatment strategies including surgery have never achieved a superior prognostic outcome to those without surgery in patients with stage III non-small-cell lung cancer. For instance, the survival outcome resulting from induction chemoradiotherapy followed by surgery for N2-IIIA non-small-cell lung cancer was comparable to that of radical chemoradiotherapy without surgery (1). This disappointing result may be partly attributable to the significantly higher treatment-related mortality rate in the group with surgery than that in that without surgery (7.9% *vs.* 2.1%) (1). More feasible and effective multimodality treatment strategies that involve surgery for locoregional lung cancer must therefore be established.

Tyrosine kinase inhibitors (TKIs) are one of the most promising therapies for driver mutation-positive lung adenocarcinoma, with a response rate of over 50% (2). In addition, many studies have emphasized the feasibility of salvage surgery after TKI treatment for advanced lung adenocarcinoma harboring a driver mutation (3-8). This favorable result may be due to the low toxicity of TKIs on normal tissues, which are unlikely to cause tissue fibrosis, such as the 'frozen hilum' induced by radiation therapy, or impaired wound healing, which potentially causes bronchopleural fistula after lobectomy (3-8). We therefore believe that a clinical trial on the simultaneous or sequential use of TKIs and cytotoxic drugs as induction therapy for driver mutation-positive adenocarcinoma, clinically diagnosed as stage III, is warranted.

In the present study, we preliminarily conducted a feasibility study of the sequential use of TKIs and cytotoxic agents in patients with clinical stage III adenocarcinoma of the lung harboring a driver gene mutation before surgical treatment.

Patients and Methods

Eligibility criteria. Patients with the following criteria were included in the study: Adenocarcinoma of stage IIIA or IIIB with no history of any prior systemic chemotherapy or TKI therapy; anaplastic lymphoma kinase (ALK) fusion gene or epidermal growth factor receptor (*EGFR*) gene mutation; presence of a measurable lesion that met the Response

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Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (9); age of 20 to 80 years old; Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; adequate organ function within 1 week before the study entry. The laboratory value requirements were as follows: hemoglobin level ≥8 g/dl, absolute white blood cell count ≥3000/mm^3, platelet count ≥100,000/mm^3, serum bilirubin level <1.5 mg/dl, serum aspartate aminotransferase and alanine aminotransferase levels <100 IU/l, and serum creatinine level <1.5 mg/dl. Patients were not eligible if they had vital organ diseases that required treatment; had another active malignancy; had received steroids for more than 4 weeks; had any evidence of interstitial lung disease; had a known sensitivity to any component of platinum, pemetrexed, or TKIs; or were pregnant or lactating.

Written informed consent was obtained from all patients before the TKI treatment. Ethical approval was obtained from the Research Ethics Committee of Kagoshima University Hospital (no. 160290).

Treatment and evaluation. Alectinib was used in patients with *ALK* rearrangement-positive disease (n=1), and either gefitinib (n=2), erlotinib (n=1), afatinib (n=3), or osimertinib (n=3) was used in the patients with *EGFR* mutation-positive disease (n=9). The starting dose was 250 mg/day for gefitinib, 150 mg/day for erlotinib, 40 mg/day for afatinib, 80 mg/day for osimertinib, and 600 mg/day for alectinib, and each dose was reduced as needed, depending on the severity of adverse events. After the administration of TKIs for at least 60 days, patients were immediately transferred to undergo cytotoxic chemotherapy using a platinum agent and pemetrexed. Prior to the administration of pemetrexed, all patients received folic acid and vitamin B12 supplementation and standard premedication with dexamethasone (10-12). Patients received 75 mg/m^2 cisplatin or calboplatin (area under the curve of 5) and 500 mg/m^2 pemetrexed every 3 weeks for two cycles. After induction chemotherapy, patients underwent surgery. Using the National Cancer Institute Common Toxicity Criteria version 4.0 (13), patients were evaluated every 21 days to assess toxicity. The tumor response was assessed using computed tomography after TKI treatment as well as after chemotherapy. The original RECIST criteria (version 1.1) were used to assess the response (9). Postoperatively, computed tomography was performed every 3 months for 1 year and every 6 months thereafter to identify recurrent diseases.

Outcome assessment. The surgical execution rate and 90-day postoperative morbidity rate and mortality rate were the primary endpoints of the study. The objective response rates after TKI, chemotherapy, and surgery and their toxicities were the secondary endpoints.

Results

Patient characteristics. Between January 2016 and December 2018, 10 eligible patients were enrolled (Figure 1). One patient had an *ALK* fusion gene, and the remaining nine patients had an *EGFR* gene mutation. The type of *EGFR* gene mutation was exon 19 deletion (Ex19del) in five cases, Leu858Arg point mutation (L858R) in four cases, and Leu861Gln point mutation (L861Q) in one case. Table I shows the patient characteristics, treatment, and treatment outcomes.

Toxicity of TKIs and chemotherapy. One patient required the transient discontinuation of gefitinib due to grade 3 liver damage, and the patient received afatinib in place of gefitinib after resolution of the liver damage (case 4). Another patient required transient discontinuation of afatinib due to a grade 3 skin rash (case 5). The patient received a half dose of afatinib after resolution of the skin rash. There were three patients with a grade 2 skin rash and two patients with grade 2 diarrhea during the administration of EGFR-TKIs, which were all able to be controlled without discontinuation of the EGFR-TKIs. Thus, all the 10 patients eventually underwent TKI treatment for more than 60 days. During the subsequent chemotherapy, we observed grade 3 neutropenia in three cases, grade 3 thrombocytopenia in one, and grade 2 liver damage in two cases. However, all 10 patients eventually underwent two cycles of designated chemotherapy.

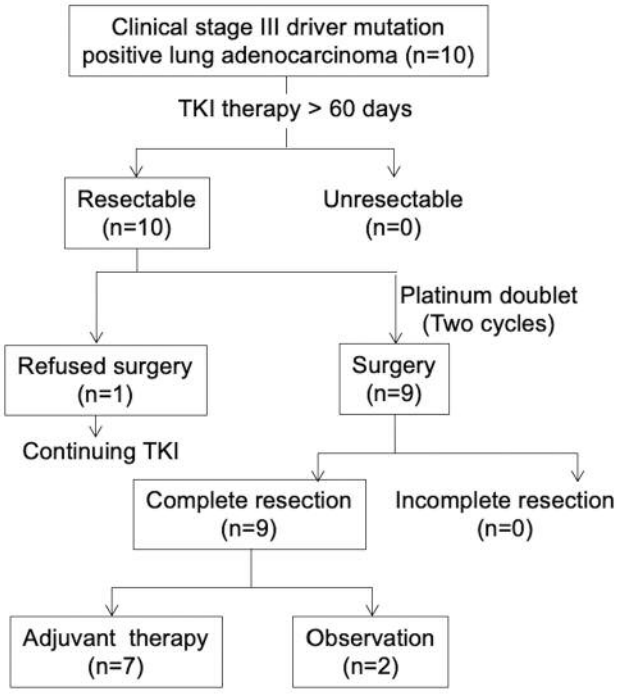

Figure 1. *Treatments of the enrolled patients (n=10). TKI: Tyrosine kinase inhibitor.*

Early surgical outcomes. All patients underwent surgery after sequential TKI and cytotoxic drug treatment, except for one who refused surgery, irrespective of their response to TKIs and chemotherapy (Figure 2). The median length from the completion of chemotherapy to surgery was 34 days (range=27-55 days). Intraoperatively, complete resection was accomplished in all nine patients by means of single lobectomy in seven, bi-lobectomy in one, and left pneumonectomy in one. Postoperatively, there was no 90-day mortality and no major postoperative complications that corresponded to grade 3 or more according to the Clavien–Dindo classification.

Table I. *Patient characteristics, treatments, and treatment outcomes.*

Case	Age, years/ gender	Driver mutation	c-TNM (stage)	TKI (days)	yc-TNM (stage)	Response to TKI	Procedure	yp-TNM (stage)	Pathological response	Adjuvant therapy	Relapse (months*)	Survival (months**)
1	59/F	*EGFR*-Ex19d	T2aN2M0 (IIIA)	Er (77)	T1aN0M0 (IA1)	PR	Lobectomy	T2aN2M0 (IIIA)	Ef. 1	CBDCA+ PEM×4→Er	None (41)	Alive (45)
2	68/M	*EGFR*-Ex19d	T2aN2M0 (IIIA)	Af (76)	T2aN0M0 (IB)	PR	Lobectomy	T1cN0M0 (IA3)	Ef. 1	None	Brain (6)	Alive (45)
3	61/M	*EGFR*-Ex21p (L858R)	T4N0M0 (IIIA)	Af (106)	T1bN0M0 (IA2)	PR	Lobectomy	T1bN0M0 (IA2)	Ef. 1	CBDCA+ PEM×2	None (32)	Alive (38)
4	75/F	*EGFR*-Ex19d	T2aN2M0 (IIIA)	Ge→Af (105)	T1bN0M0 (IA2)	PR	Lobectomy	T1bN0M0 (IA2)	Ef. 1	None	Brain (12)	Dead (21)
5	72/F	*EGFR*-Ex21p (L858R)	T3N2M0 (IIIB)	Af (84)	T2aN0M0 (IB)	PR	Lobectomy	T2aN0M0 (IB)	Ef. 1	CBDCA+ PEM×2	None (12)	Alive (17)
6	69/F	*EGFR*-Ex19d	T4N2M0 (IIIB)	Ge (88)	T2aN0M0 (IB)	PR	Lobectomy	T2aN2M0 (IIIA)	Ef. 1	CBDCA+ PEM×2	None (12)	Alive (17)
7	46/F	*EGFR*-Ex21p (L861Q)	T1bN2M0 (IIIA)	Os (84)	T1aN0M0 (IA1)	PR	Pneumo	T1miN2M0 (IIIA)	Ef. 1	CDDP+VNR ×4→Af	None (6)	Alive (11)
8	47/F	*EGFR*-Ex19d	T2bN2M0 (IIIA)	Os (245)	T2aN0M0 (IB)	PR	Bilobectomy	T2aN2M0 (IIIA)	Ef. 1	CBDCA+ PEM×2	None (2)	Alive (11)
9	73/M	*EGFR*-Ex21p (L858R)	T4N2M0 (IIIB)	Os (212)	T2aN0M0 (IB)	PR	Refused	-	-	-	-	Alive (12)
10	34/F	*ALK*	T3N2M0 (IIIB)	Al (182)	TXN0M0 (Occult)	CR	Lobectomy	TXN0M0 (Occult)	Ef. 3	CDDP+PEM ×2→Al	None (29)	Alive (38)

TKI: Tyrosine kinase inhibitor; Er: erlotinib; Af: afatinib; Ge: gefitinib; Os: osimertinib; Al: alectinib; PR: partial response; CR: complete response; Ef. 1: slight pathological response (one-third or more of viable cells); Ef. 3: complete pathological response; CBDCA: carboplatin; CDDP: cisplatin; PEM: pemetrexed; VNR: vinorelbine. *After surgery; **after treatment introduction.

Efficacy of TKIs and chemotherapy. TKI treatment resulted in a partial radiological response as well as down-staging in all 10 patients (Table I). With respect to the N-descriptor, all of the swollen mediastinal lymph nodes shrunk in nine patients who had N2 lymphadenopathy (shorter axis >1 cm) before TKI treatment. In contrast, treatment with platinum doublet resulted in stable disease in all 10 patients.

In the pathological examination of the resected specimen, TKIs and chemotherapy achieved a pathological complete response in the patient with the ALK fusion gene (case 10), while this approach resulted in a slight pathological response in all eight patients with *EGFR* mutations who had undergone surgery. Furthermore, although EGFR-TKI treatment resulted in down-staging of the N-descriptors in all patients with N2 lymphadenopathy, viable cancer cells were identified in the mediastinal lymph node in four out of the seven patients who had undergone surgery.

Short-term prognostic outcome. Seven out of the nine patients who had undergone surgery received postoperative adjuvant chemotherapy with platinum doublet, and three of them received additional TKI treatment after the chemotherapy (Table I, Figure 2). It was not possible to perform postoperative adjuvant chemotherapy in the case of two patients because of the postoperative development of interstitial lung infiltrates (case 2) or reduced physical fitness (case 4). Unfortunately, brain metastases appeared postoperatively in these two patients; one patient remains alive without further recurrence after the treatment of brain metastasis with gamma knife radiation, while the other patient died of brain metastasis that could not be treated due to a poor performance status (Figure 2). Eight out of the nine patients who underwent the designated treatment are still alive, with a median follow-up of 22 months after the initiation of the TKI treatment (Figure 2).

Discussion

We evaluated the feasibility of surgery after the sequential use of targeted therapy and chemotherapy and the impact of the preoperative treatment on the early outcomes. Our results showed that complete resection was accomplished in all nine patients who received surgery, and all of these patients recovered without postoperative major complications. Furthermore, all 10 patients who received preoperative treatment showed partial response or a better outcome, which resulted in down-staging in all of the patients. According to a pathological evaluation of the resected specimens, a complete pathological response was achieved in one patient with *ALK* rearrangement-positive disease, while a minor response was found in the remaining eight patients with

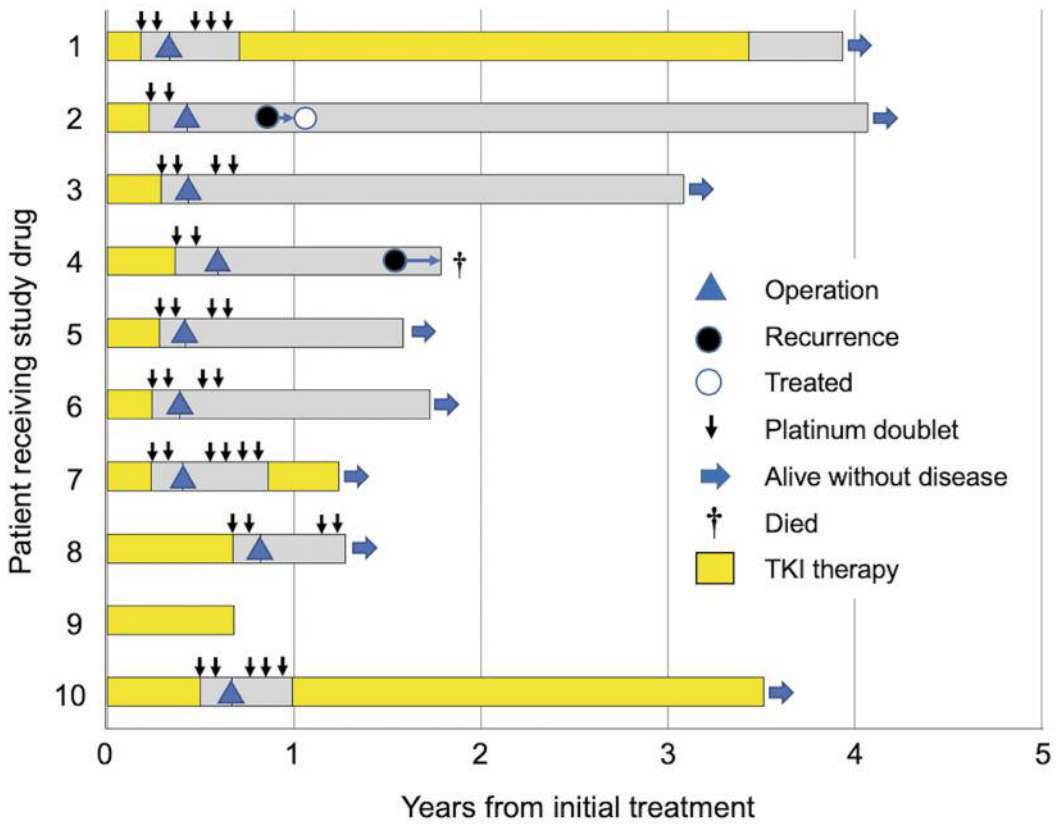

Figure 2. *Swimmer's plot of the enrolled patients (n=10). TKI: Tyrosine kinase inhibitor.*

EGFR mutation-positive disease. The low-toxicity preoperative treatment strategy used in the present study enabled postoperative adjuvant chemotherapy (and targeted therapy) in seven out of the nine patients who underwent surgery. Overall, all of the patients who underwent surgery remain disease-free after a median follow-up of 22 months since the initial treatment, with only one patient dying of recurrence. We believe that further long-term follow-up will reveal the promising effect of sequential targeted therapy and chemotherapy before surgery in patients with locally advanced EGFR mutation-positive adenocarcinoma.

Despite treatment with first- or second-generation EGFR-TKIs for a median length of 82.5 days (range=75-106 days) in five patients, no *EGFR* Thr790Met point mutation (T790M)-positive cells were detected in the resected primary tumor tissues in any of the patients. Furthermore, *EGFR* mutation-positive cells disappeared from the primary tumor in two out of the four patients who had been treated with afatinib (case 4 and case 5). Hishida *et al*. reported nine patients with advanced non-small-cell lung cancer harboring an *EGFR* mutation who underwent salvage surgery after Gefitinib treatment. In that study, T790M appeared in the resected tumor specimens in two patients who had been treated with gefitinib for more than 1 year (14), which is considerably longer than the duration for which we administered TKIs to our patients. In contrast, the third-generation EGFR-TKI, osimertinib, may have the potential to prevent drug resistance due to an T790M point mutation, thereby prolonging progression-free and overall survival compared with gefitinib (15). Unfortunately, in our study, *EGFR* mutation-positive cells were still found in the resected tumor specimens in two patients after treatment with osimertinib. Thus, the optimal TKIs for preoperative administration, as well as the optimal length of treatment, should be investigated in the future.

In the present study design, patients were scheduled to receive cytotoxic chemotherapy immediately after TKI treatment because of the following theoretical bases. Chaft *et al*. reported that disease flare, characterized by the sudden progression of the disease, occurred in 14 out of 61 patients between 3 days and 3 weeks after the discontinuation of EGFR-TKIs and that they showed a poorer prognosis than patients who did not experience disease flare (16). In our study, the immediate introduction of cytotoxic chemotherapy

after TKI treatment may have contributed to the prevention of disease flare. In addition, according to an *in vitro* study, treatment with gefitinib or erlotinib in cells expressing wild-type EGFR typically leads to G_1 cell-cycle arrest, whereas in cells expressing mutant *EGFR* it leads to pronounced apoptosis (17). Given that pemetrexed exerts a cytotoxic effect against cells in the S-phase (18) while cisplatin and carboplatin are non-phase-specific, we avoided using EGFR-TKIs and cytotoxic agents simultaneously.

Regarding *ALK* rearrangement-positive adenocarcinoma, Zhang *et al*. reported two patients in whom a pathological complete response was achieved by neoadjuvant treatment with alectinib alone among 11 patients with *ALK* rearrangement-positive locally advanced lung adenocarcinoma (19). This result, along with our own findings in case 10, may suggest that *ALK* rearrangement-positive lung cancer has different biological characteristics from *EGFR* mutation-positive lung cancer.

Whether or not adjuvant therapy improves postoperative survival in the current treatment setting with EGFR-TKI remains controversial. Previous reports described two patients who exhibited a complete pathological response after gefitinib treatment, which was confirmed after salvage surgery (5, 20). Unfortunately, one of the two patients developed brain metastasis after salvage surgery (5). In our study, two patients who were unable to receive adjuvant therapy developed brain metastasis during the postoperative follow-up period. Regarding the impact of adjuvant EGFR-TKI on the prognostic outcomes, Pennel *et al*. reported that erlotinib administration for 2 years after surgery significantly prolonged the time to recurrence compared with a matched control group and that a longer administration of erlotinib was associated with a favorable prognostic outcome (SELECT study) (21). However, whether adjuvant erlotinib contributed merely to delaying recurrence or actually improved the cure rate remains unclear. This issue will be addressed by ongoing randomized trials comparing long-term overall survival, *e.g*. the ALCHEMIST trial (NCT02193282) comparing patients treated with 2 years of adjuvant erlotinib *versus* placebo for resected stage IB to IIIA non-small-cell lung cancer harboring *EGFR* mutations and the ADAURA trial (NCT02511106) comparing patients treated with 3 years of adjuvant osimertinib *versus* placebo.

In conclusion, a radical operation after the sequential use of cytostatic and cytotoxic drugs achieved a favorable short-term outcome. Although further long-term follow-up is needed to confirm the true value of our treatment strategy, our results should prove helpful in planning large-scale study on the usefulness of neoadjuvant targeted therapy.

Conflicts of Interest

None.

Authors' Contributions

AM had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. UT, KG, TT, HTA, MK, NT, YN, KK, NY, IN, and MS contributed to the data collection and image interpretation. AM, UK, and SM contributed substantially to the study design, data analysis and interpretation, and the writing of the article. All Authors read and approved the article.

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