Original Article

Successful long-term outcome of neoadjuvant sequential targeted therapy and chemotherapy for stage III non-small cell lung carcinoma: 10 case series

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Background: Perioperative treatment of locally advanced non-small cell lung cancer (NSCLC) is attracting attention. The effect of neoadjuvant tyrosine kinase inhibitor (TKI) therapy on postoperative long-term outcomes in patients with driver gene mutations remains unclear. The aim of this study was to clarify the long-term survival outcomes of patients with stage III NSCLC harboring driver gene mutations who received preoperative TKI therapy.

Methods: Between January 2016 and December 2018, 10 patients with clinical stage III NSCLC with driver gene mutations were treated with TKIs [epidermal growth factor receptor (*EGFR*) mutation, n=9; anaplastic lymphoma kinase (*ALK*) fusion, n=1]. One patient refused surgery. The remaining nine patients received sequential chemotherapy followed by surgery. Postoperatively, six patients received adjuvant chemotherapy, and TKIs were readministered in four patients.

Results: The main adverse events of TKIs were grade 3 liver damage and grade 3 skin rash, which required a change in the drug from gefitinib to afatinib and dose reduction, respectively. In all 10 patients, the radiological response to TKIs was greater than the partial response, and nine patients underwent radical surgery. Although viable cancer cells remained in all patients with *EGFR* mutations, a pathological complete response was obtained in the patient with *ALK* fusion. No mortality or major morbidity was observed perioperatively. Of the patients who underwent surgery, 3 were alive without recurrence, while 6 had distant metastasis, including 5 with brain metastasis. Seven of the nine patients who underwent surgery were still alive after a median follow-up period of 77.2 months.

Conclusions: Successful long-term outcomes were achieved after sequential targeted therapy and chemotherapy, followed by surgery for stage III NSCLC. However, it is noteworthy that postoperative treatment may have also contributed to minimizing postoperative recurrence.

Keywords: Non-small cell lung cancer with driver gene mutation (NSCLC with driver gene mutation); stage III; neoadjuvant tyrosine kinase inhibitors (neoadjuvant TKIs); long-term survival outcome; case series

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Introduction

Non-small cell lung cancer (NSCLC) is a frequently diagnosed cancer with the highest mortality rate of all types of cancer (1). Current therapeutic approaches, including molecularly targeted agents and immune checkpoint inhibitors, have been shown to enhance outcomes in both unresectable and resectable NSCLC (2).

NSCLC is caused by several driver gene mutations, including epidermal growth factor receptor (*EGFR*) mutations that occur in 40–55% of patients, and anaplastic lymphoma kinase (*ALK*) fusion that occurs in 3–5% of East Asian patients (3). It has been reported that cytotoxic anticancer drugs and immune checkpoint inhibitors may be less effective in NSCLC patients with *EGFR* mutations (4-7). In contrast, tyrosine kinase inhibitors (TKIs), which are molecular target drugs for driver gene mutations, have a high response rate in metastatic NSCLC patients with mutations (8,9). Furthermore, osimertinib for patients with *EGFR* mutations and alectinib for patients with *ALK* fusions showed good prognosis-improving effects as adjuvant therapy (10,11). However, clinical trials using these drugs as preoperative treatment, the NeoADAURA trial (NCT04351555) and the ALNEO trial (NCT05015010), are ongoing (12,13), and their therapeutic effect is not yet known. The NeoADAURA trial will evaluate the efficacy and safety of neoadjuvant osimertinib as monotherapy or in combination with chemotherapy versus chemotherapy alone in patients with resectable stage II–IIIB N2 NSCLC with EGFR mutation, as well as adjuvant osimertinib per the investigator's choice (12).

We previously reported on patients with stage III NSCLC with driver gene mutations who received neoadjuvant TKI therapy. In the report, there were no major drug side effects that led to discontinuation of treatment, and radical surgery was performed for all patients, except for 1 patient who refused surgery. In addition, there was no surgical mortality or major morbidity, and the short-term survival outcome was good at 22 months after the initiation of treatment (see Results section). However, it is unclear whether this treatment is beneficial for long-term survival (14). We herein report long-term follow-up data collected for more than 5 years after the initiation of treatment. We present this article in accordance with the AME Case Series reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-545/rc).

Highlight box

Key findings

- Preoperative and postoperative tyrosine kinase inhibitor (TKI) treatment for clinical stage III non-small cell lung cancer (NSCLC) patients with driver gene mutation demonstrated good feasibility and achieved long-term survival.

What is known and what is new?

- Reports showing the effect of preoperative TKI administration on the survival of clinical stage III patients with driver gene mutations are limited, and the survival outcomes in those reports were not satisfactory.
- TKI therapy rarely achieved a pathological complete response, suggesting that cytotoxic anticancer drugs following surgery may be an effective therapeutic option.
- We evaluated the efficacy and survival of patients who received preoperative epidermal growth factor receptor-TKI therapy or anaplastic lymphoma kinase-TKI therapy followed by cytotoxic anticancer drugs.

What is the implication, and what should change now?

- Preoperative and postoperative treatment with TKIs and chemotherapy may help to improve long-term survival of clinical stage III NSCLC patients with driver gene mutations. In addition, oligorecurrence is an important feature of this treatment, contributing to long-term disease control with local therapy and TKI therapy.

Methods

Subjects

This study was a single-arm, prospective Phase 2 study. We enrolled consecutive patients in whom TKI therapy was started at our hospital from January 2016 to December 2018, whose background and laboratory parameters met all of the inclusion criteria. The inclusion criteria were as follows: (patient background) diagnosis of adenocarcinoma (stage IIIA or IIIB); no previous treatment with of systemic chemotherapy or TKI therapy; a measurable lesion that met the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (15); *ALK* fusion or *EGFR* mutation positivity; age, 20 to 80 years; appropriate organ function in the week prior to study entry; and Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (laboratory parameters) hemoglobin, ≥8 g/dL; absolute white blood cell count, ≥3,000/mm^3; platelet count, ≥100,000/mm^3; serum creatinine, <1.5 mg/dL; serum bilirubin, <1.5 mg/dL; and serum aspartate aminotransferase and alanine aminotransferase, <100 IU/L. Patients who

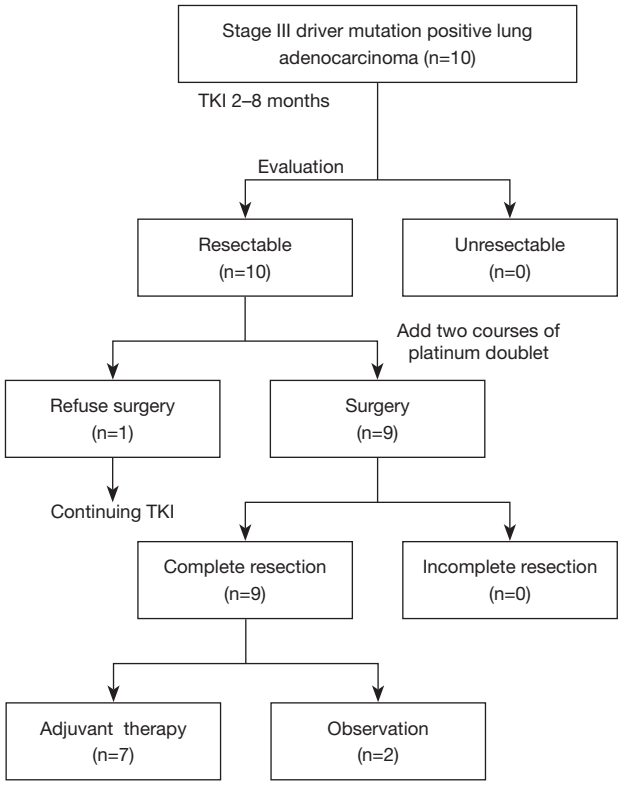

Figure 1 The diagram showing the research flow of this study. TKI, tyrosine kinase inhibitor.

met any of the following criteria were excluded from the study: other active malignancy; vital organ disease requiring treatment; evidence of interstitial lung disease; steroid therapy for more than four weeks; or known sensitivity to any component of platinum, pemetrexed, or TKIs. In addition, patients or were pregnant or lactating were excluded from the study. Before treatment, all patients received enhanced brain magnetic resonance imaging to evaluate for brain metastases and positron emission tomography (PET) to evaluate for other metastases. *EGFR* mutation was analyzed by polymerase chain reaction and *ALK* fusion was analyzed by immunohistochemistry and fluorescence *in situ* hybridization using biopsy and surgically resected specimens. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients gave their written informed consent before the start of TKI therapy. The document also included information regarding the publication of the results of this study. The present study received ethical approval from the Ethics Committee on Clinical Research, Sakuragaoka Campus, Kagoshima University (approval number: 160290).

Treatment and evaluation

Figure 1 is a diagram showing the research flow of this study. A patient with *ALK* fusion was treated with alectinib (n=1), while patients with *EGFR* mutations (n=9) were treated with afatinib (n=3), osimertinib (n=3), gefitinib (n=2), or erlotinib (n=1). Treatment was initiated with the following starting doses: alectinib (600 mg/day), afatinib (40 mg/day), osimertinib (80 mg/day), gefitinib (250 mg/day), and erlotinib (150 mg/day). After ≥60 days of TKI treatment, the patients were immediately transferred to receive cytotoxic chemotherapy (platinum agent and pemetrexed). All patients received folic acid and vitamin B12 supplementation and standard premedication with dexamethasone before they received pemetrexed (16-18). The patients received cisplatin or carboplatin (75 mg/m^2; area under the curve: 5) and pemetrexed (500 mg/m^2) every 3 weeks for 2 cycles. Surgery was performed after the completion of induction chemotherapy. Patients were evaluated for toxicities every 21 days according to the National Cancer Institute Common Toxicity Criteria version 4.0 (19). The dose of each drug was reduced or changed to another drug depending on the severity of the adverse events. Patients received adjuvant chemotherapy postoperatively when possible, and the restart of TKI therapy was left to the discretion of the attending physician.

The Union for International Cancer Control TNM Classification of Malignant Tumors, 8th Edition was used for clinical and pathological staging (20). Computed tomography was performed after TKI treatment and after chemotherapy to assess the tumor response, which was evaluated according to the original RECIST criteria (version 1.1) (15). After surgery, computed tomography scans were conducted every 3 months for the first year and then every 6 months to monitor for any signs of disease recurrence. The pathological effects of neoadjuvant therapy were classified based on The Japan Lung Cancer Society criteria as follows: Ef. 0, no effect; Ef. 1a, very slight effect (viable cancer cells in 67% or more of the tumor tissue); Ef. 1b, slight effect (viable cancer cells in more than 33% but less than 67% of the tumor tissue); Ef. 2, moderate effect (viable cancer cells in less than 33% of the tumor tissue with severe degeneration or necrosis of other cancer cells), and Ef. 3, strong effect (no evidence of viable cancer cells) (21).

Statistical analysis

We previously reported the early surgical outcome of this

Table 1 Patient characteristics, treatment, and treatment outcomes

Case No.	Age (years)/ gender	c-TNM (stage)	TKIs [days]	yc-stage	Radiological response	Procedure	yp-stage	Pathological effect†	Mutation status		Post-ope
									Pre-ope	Post-ope	Plasma test
Case 1	59/F	T2aN2M0 (IIIA)	E [77]	T1aN0M0 (IA1)	PR	Lobectomy	T2aN2M0 (IIIA)	Ef. 1a	Ex19d	Ex19d	–
Case 2	68/M	T2aN2M0 (IIIA)	A [76]	T2aN0M0 (IB)	PR	Lobectomy	T1cN0M0 (IA3)	Ef. 1a	Ex19d	Ex19d	Not tested
Case 3	61/M	T4N0M0 (IIIA)	A [106]	T1bN0M0 (IA2)	PR	Lobectomy	T1bN0M0 (IA2)	Ef. 1a	L858R	L858R	Not tested
Case 4	75/F	T2aN2M0 (IIIA)	G→A [105]	T1bN0M0 (IA2)	PR	Lobectomy	T1bN0M0 (IA2)	Ef. 1a	EX19d	–	Not tested
Case 5	72/F	T3N2M0 (IIIB)	A [84]	T2aN0M0 (IB)	PR	Lobectomy	T2aN0M0 (IB)	Ef. 1b	L858R	–	Not tested
Case 6	69/F	T4N2M0 (IIIB)	G [88]	T2aN0M0 (IB)	PR	Lobectomy	T2aN2M0 (IIIA)	Ef. 1a	Ex19d	Ex19d	Not tested
Case 7	46/F	T1bN2M0 (IIIA)	O [84]	T1aN0M0 (IA1)	PR	Pneumonectomy	T1miN2M0 (IIIA)	Ef. 1a	L861Q	L861Q	–
Case 8	47/F	T2bN2M0 (IIIA)	O [245]	T2aN0M0 (IB)	PR	Bilobectomy	T2aN2M0 (IIIA)	Ef. 1a	Ex19d	Ex19d	Not tested
Case 9	73/M	T4N2M0 (IIIB)	O [212]	T2aN0M0 (IB)	PR	Refuse surgery	Refuse surgery	Unevaluable	L858R	Unevaluable	Unevaluable
Case 10	34/F	T3N2M0 (IIIB)	Al [182]	TXN0M0 (Occult)	CR	Lobectomy	TXN0M0 (occult)	Ef. 3	ALK	Not tested	Not tested

†, Ef. 1a: very slight effect (viable cancer cells in ≥67% of the tumor tissue); Ef. 1b: slight effect (viable cancer cells in ≥33% to <67% of the tumor tissue); Ef. 3: strong effect (no evidence of viable cancer cells). TKIs, tyrosine kinase inhibitors; Pre-ope, pre-operation; Post-ope, post-operation; F, female; E, erlotinib; PR, partial response; M, male; A, afatinib; G, gefitinib; O, osimertinib; CR, complete response; Al, alectinib.

treatment (14). The main purpose of this study was to analyze the long-term outcomes of this treatment. The reverse Kaplan-Meier method was used to estimate the median follow-up period was estimated using. Disease-free survival (DFS) was defined as the period from the date of surgery until the date of recurrence, and censored in cases without events at the time of their last clinic visit. Overall survival (OS) was defined as the interval from the date of initiation of TKI therapy until the date of death from any cause, censored for patients who were alive at the last clinic visit. EZR ver.1.61 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used to perform all statistical analyses.

Results

Patient characteristics

Ten consecutive patients who initiated TKI treatment between January 2016 and December 2018 were enrolled in this study. *Table 1* shows the patient characteristics, treatment, and treatment outcomes. *Table 2* shows the changes in tumors and lymph node metastases before and after preoperative treatment, as well as detailed pathological findings. There were three male and seven female patients with median age of 64.5 years (range, 34–75 years). 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 (Ex19d) in five patients, Leu858Arg point mutation (L858R) in three patients, and Leu861Gln point mutation (L861Q) in 1 patient. The surgical procedures were lobectomy in seven patients (Cases 1, 2, 3, 4, 5, 6, 10), bilobectomy in one patient (Case 8), and pneumonectomy in one patient (Case 7). Complete resection was achieved in all patients except for one patient who refused surgery.

Toxicity of drugs and short-term surgical outcome

We previously reported the surgical execution rate, 90-day postoperative morbidity and mortality, objective response rates after TKIs and chemotherapy, and their toxicity (14). The main adverse events of TKIs were grade 3 liver damage (Case 4) and grade 3 skin rash (Case 5), which required a change in the drug from gefitinib to afatinib and dose reduction, respectively. Preoperative evaluation showed downstaging in all patients, and the radiological response was partial response (PR) in all patients with *EGFR* mutation and complete response (CR) in a patient with *ALK* fusion. Nine patients underwent radical surgery, excluding one patient who refused surgery (Case 9), and no mortality or major morbidity was observed within 90 days after surgery.

Pathological assessment

Eight of the nine patients who underwent surgery had

Table 2 Preoperative treatment-induced changes in tumors and lymph node metastases and detailed pathological findings

Case No.	Tumor size before treatment (mm)	Positive node before treatment [number]	Modalities for evaluating positive node	Tumor size before surgery (mm)	Pathological tumor size (mm)	pl	ly	v	Total dissected node number	Pathological positive node [number]
Case 1	57	4R [1], 12u [1]	CT, PET, EBUS-TBNA	24	15	1	1	1	7	4R [1]
Case 2	23	4L [1], 12u [2]	CT, PET	16	30	0	0	0	23	None
Case 3	55	None	N/A	16	43	0	0	0	18	None
Case 4	24	9L [1]	CT, PET	15	15	0	0	0	11	None
Case 5	34	4R [1], 12u [1]	CT, PET, EBUS-TBNA	21	31	0	1	0	31	None
Case 6	41	5 [1]	CT, PET	26	26	2	1	1	9	5 [1]
Case 7	15	4L [1], 6 [1], 11 [2], 12u [1], 12L [3]	CT, PET, EBUS-TBNA	6	19	1	1	1	28	2R [1], 3a [2], 4R [5], 10L [2], 11s [3], 13m [1]
Case 8	46	4R [1], 11s [1]	CT, PET	27	15	0	1	0	19	4L [4], 6 [3], 10L [3], 11 [1], 12u [1], 12l [4]
Case 9	75	4L [1], 10 [1]	CT, PET, EBUS-TBNA	33	N/A	N/A	N/A	N/A	N/A	N/A
Case 10	50	4R, 7, 12u [involve]	CT, PET	0	0	0	0	0	12	None

pl, pleural invasion; ly; lymphatic invasion; v, vascular invasion; CT, computed tomography; PET, positron emission tomography; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; N/A, not applicable.

lymph node metastasis before treatment, but all patients were evaluated as having no metastasis in the preoperative evaluation. *Figure 2* shows the changes in PET images before and after preoperative treatment in two patients (Cases 5 and 7). However, metastasis was found in the dissected lymph nodes of four patients. Furthermore, although a pathological complete response was obtained in patients with *ALK* fusions, residual viable cancer cells were observed in patients with *EGFR* mutations. When we searched for *EGFR* mutations using resected specimens from all eight patients with *EGFR* mutations who underwent surgery, the thr790met point mutation (T790M) was not detected. Additionally, in two patients, *EGFR* mutations detected before treatment were not detected after surgery (Cases 4 and 5). Furthermore, in two patients, we searched for *EGFR* mutations in the plasma between surgery and adjuvant therapy, and the results were negative in both patients (Cases 1 and 7).

Long-term outcome

Figure 3 shows a swimmer's plot of the progress of all patients enrolled in this study after the initiation of TKI therapy. One patient who refused surgery continued to receive osimertinib for 30.1 months, but died 33.5 months after the initiation of treatment (Case 9). The 5-year DFS after surgery for the nine patients who underwent surgery was 29.6%, and the median DFS was 33.2 months. Furthermore, the 5-year OS rate after TKI initiation was 88.9%, and the median OS was not reached. After surgery, six patients received adjuvant therapy using cytotoxic anticancer drugs (Cases 1, 3, 5, 6, 7, and 10), and TKI therapy was restarted in four patients (Cases 1, 7, 8, and 10). Three patients were alive without recurrence (Cases 5, 8, and 10), but six patients had distant metastases (Cases 1, 2, 3, 4, 6, and 7), including 5 with brain metastases (Cases 1, 2, 4, 6, and 7). In patients in whom TKI therapy was not restarted postoperatively, brain metastases were observed in three patients (Cases 2, 4, and 6) and lung metastases in 1 patient (Case 3). Even in two patients who had restarted TKI treatment, brain metastasis recurrence was observed 47.4 months after the administration of erlotinib (Case 1), and 6.6 months after the administration of afatinib (Case 7). In both patients, plasma was analyzed to detect *EGFR* mutations before restarting TKI therapy after surgery, but no mutations were detected. Case 1 developed brain metastasis while receiving erlotinib after surgery and was treated with gamma knife. However, the tumor recurred

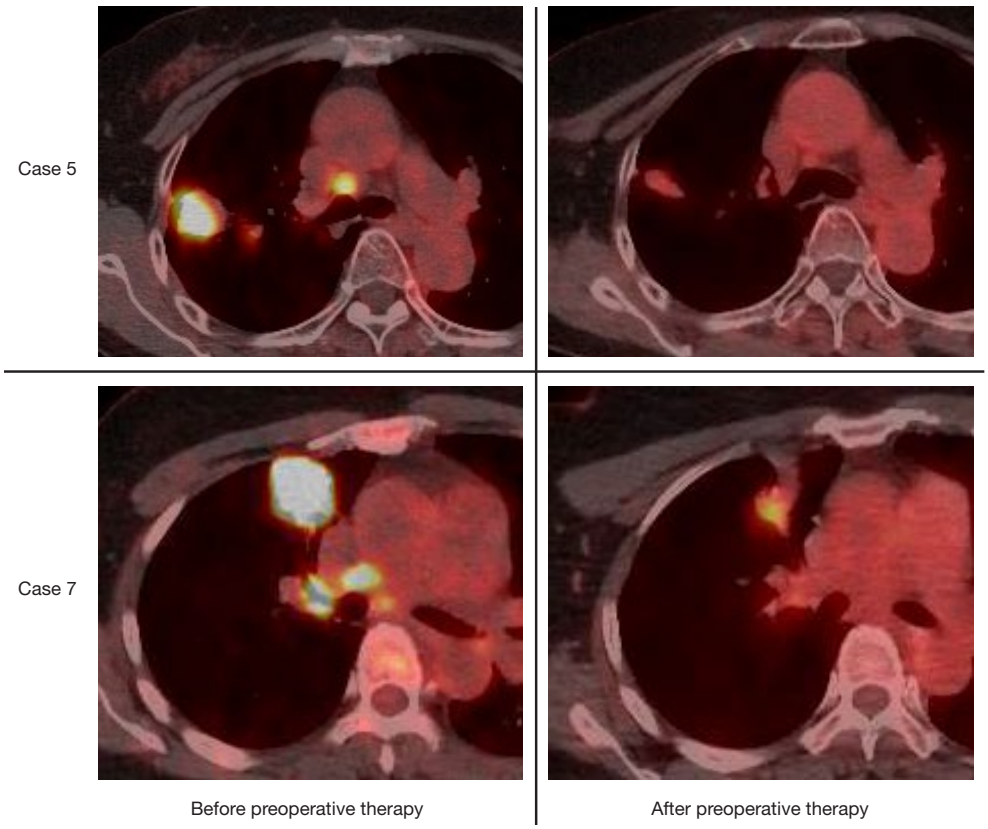

Figure 2 The changes in PET images before and after preoperative treatment in two patients (Cases 5 and 7). PET, positron emission tomography.

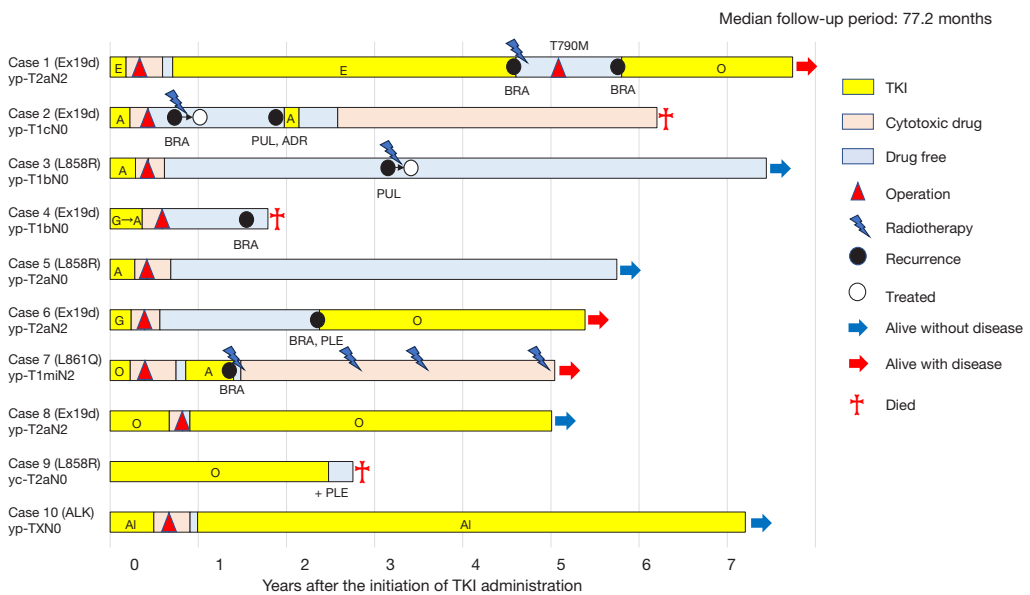

Figure 3 Swimmer's plot showing the progress of all patients enrolled in this study after the initiation of TKI therapy (n=10). TKI, tyrosine kinase inhibitor; E, erlotinib; O, osimertinib; BRA, brain metastasis; A, afatinib; PUL, pulmonary metastasis; ADR, adrenal metastasis; G, gefitinib; PLE, pleural dissemination; Al, alectinib.

and she underwent brain metastasectomy. T790M mutation was detected in the resected specimen, so she is currently continuing treatment with osimertinib. In two patients who were not able to receive any adjuvant therapy due to postoperative physical deterioration, recurrence of brain metastasis was observed in the early postoperative period (Cases 2 and 4). At present, a median follow-up period of 77.2 months has passed since the initiation of treatment, and seven of the nine patients who underwent surgery are still alive.

Discussion

In this study, we report the long-term outcomes of clinical stage III NSCLC patients with driver gene mutations who received preoperative TKI therapy followed by cytotoxic anticancer drugs. After a median follow-up period of 77.2 months after the initiation of TKI therapy, 8 of the 9 (88.9%) patients who underwent surgery achieved 5-year survival, and 7 (77.8%) patients were still alive. Our treatment strategy was both feasible and effective in achieving long-term disease control in patients with oligometastasis. Preoperative and postoperative treatment with TKIs and chemotherapy potentially contribute to improved long-term survival outcomes.

According to a large-scale analysis of surgical patients conducted in Japan, the 5-year DFS and 5-year OS rates of patients with clinical stage IIIA NSCLC (according to the TNM 8th edition), including patients with driver mutation-negative disease, were approximately 39% and 50%, respectively (22). In contrast, according to the current study on driver gene mutation-positive disease, the 5-year DFS rate after surgery was poorer (29.6%), while the 5-year OS was better (88.9%). The discrepancy in DFS may be attributable to the differences in clinical aggressiveness between EGFR mutation-positive disease and EGFR mutation-negative disease, and previous studies have suggested that patients with relatively advanced NSCLC with *EGFR* mutations have worse DFS than those without *EGFR* mutations (23,24), while patients with *EGFR* mutations had better DFS than those without mutations among Japanese patients with NSCLC who underwent surgery (25).

To the best of our knowledge, only 2 reports have demonstrated the effect of preoperative TKI treatment on survival in clinical stage III patients with *EGFR* mutations. Xiong *et al.* conducted a single-arm clinical trial of neoadjuvant therapy with erlotinib, a first-generation *EGFR*-TKI, for clinical N2 stage IIIA NSCLC with *EGFR* mutations and reported a median DFS of 10.5 months (26). Zhong *et al.* conducted a clinical trial comparing erlotinib and chemotherapy as preoperative treatments for clinical N2-stage IIIA NSCLC with *EGFR* mutations. In this trial, erlotinib demonstrated significantly better efficacy in prolonging DFS in comparison to chemotherapy. The median DFS, 5-year DFS, median OS, and 5-year OS were 21.5 months, 8.1%, 42.2 months, and 40.8%, respectively (27). The median DFS in our study was 33.2 months and the 5-year DFS rate was 29.6%, which was better than the results of the 2 previous studies. One possible explanation for this difference is the types of *EGFR*-TKIs that were used for preoperative treatment. In the FLAURA trial conducted for metastatic NSCLC with *EGFR* mutations, osimertinib, a third-generation *EGFR*-TKI, significantly prolonged progression-free survival and OS in comparison to a first-generation *EGFR*-TKI (8). In our study, three patients received preoperative treatment with a first-generation *EGFR*-TKI (Cases 1, 4, and 6), and 1 was changed to a second-generation *EGFR*-TKI due to an adverse event (Case 4). In total, second-generation TKIs were used in 4 cases (Cases 2, 3, 4, and 5), and third-generation TKIs were used in 2 cases (Cases 7 and 8). Better results may have been obtained if the preoperative treatment was standardized with osimertinib. In this regard, the results of the ongoing NeoADAURA trial are promising (12).

In the preoperative treatment of this study, cytotoxic anticancer agents were used sequentially after TKIs. To date, only one case of a pathologic complete response to treatment with TKI alone has been documented (28). This finding suggests that *EGFR* mutation-positive lung cancer cells in lung cancer tissue are not monoclonally proliferating, but rather that heterogeneity exists. Furthermore, *in vitro* studies have shown that EGFR mutant cell lines induced significant apoptosis upon exposure to gefitinib, whereas *EGFR* wild-type cell lines sensitive to gefitinib induced G1-S arrest (29). Because pemetrexed exerts cytotoxicity on cells in the S phase (30), the present study avoided the simultaneous use of TKIs and cytotoxic anticancer agents. However, recent study has shown promising results with concurrent osimertinib and cytotoxic agents in metastatic NSCLC patients with *EGFR* mutations (31). The NeoADAURA trial was designed to administer osimertinib in concurrent combination with cytotoxic agents prior to surgery, and the result is attracting attention.

Oligorecurrence after radical resection of driver gene mutation-positive lung cancer can be treated with local or

systemic therapy with favorable postrecurrence survival outcomes (32,33). In the present study, the majority of patients who underwent radical resection following neoadjuvant therapy developed recurrent disease; however, it was oligorecurrence. The 5-year OS rate was 88.9%, which was thought to be due to the combined effects of preoperative and postoperative treatments as well as a multidisciplinary approach involving local and systemic therapies for the treatment of oligorecurrence.

However, whether postoperative adjuvant therapy should be administered to patients who receive preoperative therapy remains controversial. White *et al.* reported that patients with N2 NSCLC who received preoperative therapy may benefit from adjuvant chemotherapy (34). In our study, most patients received adjuvant therapy with cytotoxic anticancer drugs, but two patients who did not receive adjuvant therapy developed recurrence relatively early (Cases 2 and 4). This indicates the need for adjuvant therapy with cytotoxic anticancer drugs. Additionally, four patients in our study restarted TKI therapy postoperatively (Cases 1, 7, 8, and 10). In the ADAURA trial, administration of osimertinib for 3 years after surgery significantly prolonged 5-year OS in patients with stage II–IIIA disease, and the difference was more pronounced in stage III disease (10). However, it is unclear whether postoperative adjuvant therapy, such as TKIs, should be added for patients who have already received TKI treatment before surgery. The NeoADAURA trial (12) could offer new insights into this matter.

One of the key clinical challenges at present is identifying the factors that indicate which patients require further adjuvant therapy after surgery. In this study, the brain was the first site of recurrence in five of six patients with recurrence (Cases 1, 2, 4, 6, and 7). Brain metastasis have been reported to be common in patients with *EGFR* mutations (35,36). Suda *et al.* reported that the incidence of postoperative recurrence of brain metastasis was significantly higher in patients with *EGFR* mutations than in those without EGFR mutations (25). In our study, *EGFR* mutations were not detected in two patients who were tested for plasma *EGFR* mutations between surgery and the initiation of postoperative treatment; however, both patients developed brain metastasis (Cases 1 and 7). Romero *et al.* tested for plasma *EGFR* mutations in 22 patients who developed resistance to the T790M mutation during treatment with first- and second-generation *EGFR*-TKIs and had metastasis to various organs. No plasma *EGFR* mutations were detected in three of the 22 patients. Interestingly, two of the three patients had brain metastasis (37). This finding suggests that the current plasma *EGFR* mutation test cannot fully predict brain metastasis, which is often the site of recurrence in patients with *EGFR* mutations. In the future, it is hoped that more accurate markers will be developed to determine whether patients should receive adjuvant therapy.

It is extremely rare to obtain a pathological complete response during surgery after using *EGFR*-TKIs (28). In this study, preoperative treatment achieved downstaging and a radiological PR in all patients; however, in patients with *EGFR* mutations, residual cancer cells were observed in all resected specimens. In addition, *EGFR* mutations were not detected in the surgical specimens of two of the eight patients with *EGFR* mutations who underwent surgery. This may represent intratumoral genetic heterogeneity and resulting treatment resistance (38). In such cases, there is little benefit of continuing EGFR-TKI treatment with *EGFR*-TKIs. Stage III NSCLC needs to be treated as equivalent to systemic disease, and it has been shown that adding local therapy, including surgery, to the treatment process contributes to improving the prognosis, even in patients with *EGFR* mutations.

The resected specimen from the patient with *ALK* fusion showed a pathological complete response, and alectinib was continued postoperatively without recurrence. Sentana-Lledo *et al.* reported two patients with *ALK* fusion, in which complete resection was performed after the administration of alectinib (39). One patient had a pathological complete response and the other had a pathological major response. The former patient continued alectinib after surgery without recurrence, but the latter did not continue TKI therapy and developed recurrence. Two clinical trials are currently underway to examine the effects of alectinib as a perioperative treatment for patients with *ALK* fusions (11,13). These trials will provide more robust evidence-based data for alectinib as a perioperative treatment for patients with *ALK* fusions. The effects of molecular-targeted drugs vary depending on the driver gene mutation, and it is necessary to subdivide treatments according to specific gene mutations in the future.

TKIs can be safely used during preoperative therapy. In a meta-analysis summarizing previous neoadjuvant trials with *EGFR*-TKIs, Shi *et al.* reported that the rate of grade 3–4 adverse events with *EGFR*-TKIs was 0%, and the surgical rate was 95% (40). In our study, there were no patients in whom treatment could not be continued because of adverse events caused by preoperative treatment. In addition, radical resection was possible in all patients except for 1

patient who refused surgery. There was no mortality or major morbidity due to surgery, and the feasibility of this treatment was considered to be good.

Limitations

The most significant limitation associated with this study was the fact that it was conducted at a single institution with a small number of patients. It would be desirable to study more patients in a wider geographical area, including people of various ethnicities. In this study, the preoperative TKIs treatment period was set at 60 days or more. While TKIs usually acquire resistance within about one year, they have a tumor shrinking effect from an early stage of treatment. The actual median preoperative TKIs treatment period was 88 days (range, 96–245 days), and a good tumor shrinkage effect was obtained. However, in all patients with EGFR mutations, tumor cells remained in the resected specimens. At present, the optimal preoperative TKIs treatment period is unknown, and further research is required to clarify this. In this study, of the four patients who were assessed as pN0 on postoperative pathological findings but were assessed as cN2 before treatment, two patients (Cases 2 and 4) did not receive preoperative histological evaluation of lymph nodes. Both of these patients died of cancer due to postoperative recurrence, but pretreatment histological evaluation of lymph nodes is very important in patients received preoperative therapy.

Conclusions

For patients with stage III NSCLC with driver gene mutations, surgery was performed after preoperative treatment with TKIs, and good feasibility and long-term survival were confirmed. However, since many patients experience recurrence after surgery, it is important to provide postoperative treatment to suppress recurrence and to identify patients who require such treatment. The findings of our study suggest the potential for the development of a new treatment option, which should be subjected to a large-scale evaluation.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-545/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-545/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients gave their written informed consent before the start of TKI therapy. The document also included information regarding the publication of the results of this study. Ethical approval was obtained from the Ethics Committee on Clinical Research, Sakuragaoka Campus, Kagoshima University (approval number 160290).

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