in vivo *34*: 247-253 (2020)
doi:10.21873/invivo.11767

Adverse Events of Concurrent Radiotherapy and ALK Inhibitors for Brain Metastases of ALK-Rearranged Lung Adenocarcinoma

TAKAAKI NAKASHIMA[1,2], TAKESHI NONOSHITA[2], HIDENARI HIRATA[1], KOUJI INOUE[3], AKIRA NAGASHIMA[4], TADAMASA YOSHITAKE[1], KAORI ASAI[1] and YOSHIYUKI SHIOYAMA[1]

[1]*Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan;*
[2]*Department of Radiology, Kitakyushu Municipal Medical Center, Kitakyushu, Japan;*
[3]*Department of Respiratory Medicine, Kitakyushu Municipal Medical Center, Kitakyushu, Japan;*
[4]*Department of Thoracic Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan*

Abstract. *Background: We investigated acute adverse events in patients with brain metastases (BMs) of anaplastic lymphoma kinase-rearranged (ALKr) non-small cell lung cancer (NSCLC) treated with both cranial radiotherapy and tyrosine kinase inhibitors (TKIs) of ALK. Patients and Methods: Acute AEs were retrospectively investigated in patients with BMs of ALKr-NSCLC who received both whole-brain radiotherapy (WBRT) and ALK-TKI. For comparison, they were also assessed in patients with epidermal growth factor receptor (EGFR)-mutated NSCLC and wild-type with neither ALK rearrangement nor EGFR mutation treated with WBRT. Results: Two ALKr cases were consequently eligible. Grade 3 otitis media unexpectedly occurred in both cases, while there was one case out of 11 and one case out of 18 of grade 2 otitis media among the EGFR-mutated cases and wild-type cases (p=0.013), respectively. Conclusion: Concurrent treatment with WBRT and ALK-TKI may be associated with acute severe ear toxicity in patients with BMs of ALKr-NSCLC.*

Anaplastic lymphoma kinase gene rearrangement (*ALKr*) is a significant driver of gene mutation for novel molecular-targeted therapy in lung cancer, and is identified in about 2-7% of non-small cell lung cancer (NSCLC) cases (1). The predominant histological subtype in *ALKr* NSCLC is adenocarcinoma, and *ALKr* is rarely seen in other histological subtypes, including small-cell lung cancer. In addition, unlike mutation of epidermal growth factor receptor (*EGFR*), which differs in humans according to race, there is no race-related difference in the frequency of *ALKr*. With regard to the prognostic significance of *ALKr*, some investigations have reported *ALKr* itself to be a favorable prognostic factor (2).

The existence of brain metastases (BMs) is a major factor leading to poor survival outcome in NSCLC, with the median survival of patients with BMs ranging from 3 to 14.8 months according to diagnosis-specific graded prognostic assessment (3). The incidence of BMs from *ALKr* NSCLC ranges from approximately 25% to 35%; it is greater than that for those with wild-type NSCLC, and slightly higher or equivalent to that of NSCLC with *EGFR* mutation (4). BMs seem to be more commonly detected at initial diagnosis in those with ALKr NSCLC compared with those with wild-type NSCLC.

Many previous clinical trials reported that multi-targeted receptor tyrosine kinase inhibitors (TKIs) of ALK, such as crizotinib, alectinib and ceritinib, achieved better local control of BMs and intracranial progression-free survival (IPFS) in *ALKr* NSCLC (5-7). Crizotinib, a first-generation ALK-TKI, was associated with a median IPFS of 7 months in patients with BMs that was previously untreated in the analysis of PROFILE 1005 and 1007 (8). After the experience of progression with a single ALK-TKI, it is promising to consider sequential therapy with multiple ALK-TKI (9-12). Regardless of the efficacy of ALK-TKI for BMs, it is concerning that many patients invariably develop progression of intracranial disease. Therefore, radiotherapy such as whole-brain radiotherapy (WBRT) and stereotactic irradiation plays an essential role in the local control of BMs in *ALKr* NSCLC.

Correspondence to: Takaaki Nakashima, MD, Department of Clinical Radiology, Kyushu University Graduate School of Medical Sciences, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan. Tel: +81 926425695, Fax: +81 926425708, e-mail: takaaki813@hotmail.co.jp

Key Words: ALK-TKI, radiotherapy, adverse events, lung adenocarcinoma, brain metastases.

However, there are no definite guidelines for the optimal treatment strategy for BM in *ALKr* NSCLC. While recent new-generation ALK-TKIs have demonstrated promising results for BMs in terms of their efficacy in clinical studies, many details regarding the role of radiotherapy in the treatment of BMs in patients with *ALKr* remain unclear. Radiotherapy is considered to destroy the blood–brain barrier, reduce P-glycoprotein expression, and enhance the infiltration of ALK-TKI into the brain tissue, therefore radiotherapy can improve the efficacy of ALK-TKI for BMs (13). In addition, one investigation indicated that ALK-TKI acted as a radiation sensitizer in cells harboring the echinoderm microtubule-associated protein-like 4 (*EML4*)–*ALK* fusion (14). Therefore, radiotherapy combined with ALK-TKI might also be an appropriate treatment for BMs in patients with *ALKr* NSCLC. In a retrospective study, extended survival was reported in patients with BMs of *ALKr* NSCLC as a result of multidisciplinary treatment mainly involving the combination of ALK-TKI and radiotherapy (15).

Radiotherapy and ALK-TKI are generally administered sequentially because of concern about provoking worse adverse events (AEs) when they are administered concurrently. There is also a significant risk of extracranial disease flare during the withdrawal of ALK-TKI (16). AEs permitting, it might be possible to administer both treatments concurrently; however, there have been no clinical studies discussing AEs under such concurrent therapy.

Herein we describe AEs that occurred due to the combination of radiotherapy and ALK-TKI. Consequently, we discuss the tolerability of combined radiotherapy and ALK-TKI and how to combine radiotherapy and ALK-TKI in patients with BMs of *ALKr* NSCLC.

Patients and Methods

Patients. The present study was retrospectively performed using electronic medical records at Kitakyushu Municipal Medical Center and was approved by the Ethical Review Board of our Institution (no. 201703062). Between July 23, 2011 and November 1, 2016, 211 patients were histologically proven to have lung adenocarcinoma and were treated at our hospital. Eighty-one patients were diagnosed with BMs by magnetic resonance imaging, or computed tomography (only 1 case). In this population, *ALKr* was identified in six patients, and five of these with BMs were treated with both radiotherapy and ALK-TKI. Finally, three patients with *ALKr* were treated with WBRT and ALK-TKI concurrently. There were 31 patients with *EGFR*-mutated disease. Nineteen patients were treated with both radiotherapy and EGFR-TKI, including 11 who were treated concurrently. Forty-four patients were wild-type cases, *i.e.* they had neither *ALKr* nor *EGFR* mutation, and 34 of these patients were treated with radiotherapy. No patient had both ALKr and *EGFR* mutation. The detection of *ALKr* was performed using both immunohistochemistry and fluorescence in situ hybridization (FISH) in four out of five patients; for the remaining patient, only the FISH test was performed. Immunohistochemistry was performed with ALK Detection Kit (Nichirei Bioscience, Tokyo, Japan) (17). The FISH test was performed using a break-apart assay (Vysis LSI ALK Dual Color, Break Apart Rearrangement Probe; Abbott Molecular, Abbott Park, IL, USA). Patients without WBRT, those with follow-up periods of 1 month or more, or without detailed clinical records were consequently excluded from the present study (Figure 1).

The patient characteristics collected for each patient included age, sex, Eastern Cooperative Oncology Group performance status, smoking history, number of BMs, size of largest BM, symptoms from BMs, presence of leptomeningeal dissemination, extracranial metastases at initial diagnosis of BM, staging and presence of BMs at initial diagnosis, and whether or not TKI was initiated before BM diagnosis in patients with *ALKr* or *EGFR* mutation. The following treatment data were also recorded: radiotherapy method, dose/fraction of radiotherapy, and initial therapy for BM (Table I). In patients with *ALKr*, clinical outcomes were also confirmed: overall survival (OS), IPFS, and treatment response of BMs. OS was defined from the date of the initial diagnosis of BM to death. IPFS was defined from the date of the initial diagnosis of BM to the first intracranial progression. In this investigation, the calculation of survival outcomes was performed until the end of February 2017. The treatment response of BMs was assessed by magnetic resonance imaging with the use of Response Evaluation Criteria in Solid Tumors (RECIST), version 1. 1 (18).

Evaluation of AEs. AEs were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (19), and documented as the highest grade experienced. Three patients with *ALKr* were treated with both radiotherapy and ALK-TKI concurrently, and all of them received WBRT. In the present study, acute AEs after WBRT were primarily assessed in patients with *ALKr* treated with both WBRT and ALK-TKI concurrently. In addition, for comparison, acute AEs were also investigated in patients with *EGFR* mutation treated with WBRT and EGFR-TKI concurrently and patients with wild-type disease treated with WBRT solely. Herein, acute AEs after WBRT that were assessed included dermatitis, hematotoxicity, and ototoxicity. Dermatitis and hematotoxicity were assessed within 1 month and ototoxicity was assessed within 3 months from the end of radiotherapy. In this study, the term dermatitis refers to dermatitis of the scalp within the irradiated field. Hematotoxicity included leukopenia, anemia, and thrombocytopenia. Ototoxicity included *otitis media* and *externa*, and a record of an otolaryngologist's examination was required for confirmation of the diagnosis.

Radiotherapy and ALK-TKI. In the present study, WBRT was basically indicated for those with multiple BMs, and the standard dose was 30 Gy in 10 fractions with a 10-MV photon beam delivered by a Siemens Oncor linear accelerator (Siemens Healthcare, Erlangen, Germany). Another dose schedule of 35 Gy in 14 fractions was adopted for patients with a previous history of stereotactic irradiation for BMs. In one patient, 40 Gy in 20 fractions was adopted. During WBRT, steroids and osmotic diuretics were administered to most patients for the prophylaxis of acute AEs due to radiotherapy or clinical symptoms.

Patients with *ALKr* were treated with crizotinib as the first ALK-TKI in the present study. After disease progression occurred under treatment with crizotinib, alectinib was administered as the second-line ALK-TKI. One patient was subject to disease progression after

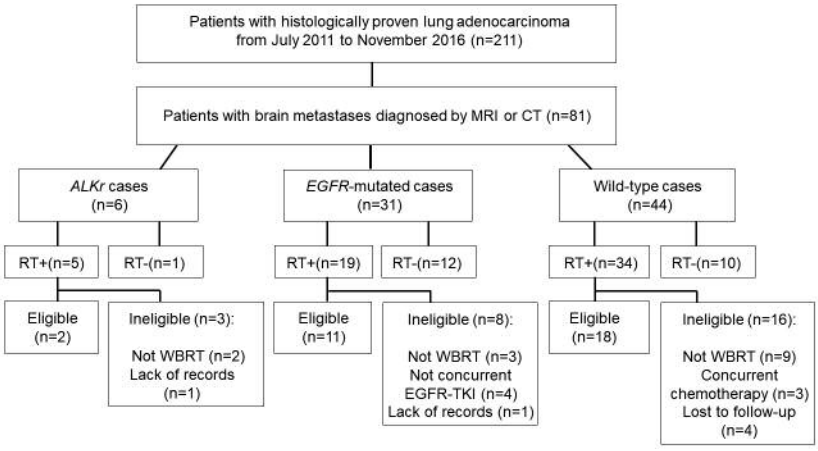

Figure 1. *Flowchart of patient selection. ALKr: Anaplastic lymphoma kinase-rearranged; CT: computed tomography; EGFR: epidermal growth factor receptor; MRI: magnetic resonance imaging; TKI: tyrosine kinase inhibitor; RT: radiotherapy; WBRT: whole-brain radiotherapy.*

switching to alectinib, and therefore ceritinib was administered. The initial daily dosage of crizotinib was 500 mg, that of alectinib was 600 mg, and that of ceritinib was 750 mg; dose reductions were determined by physicians for each patient for reasons such as AEs and renal dysfunction.

Statistical analysis. Categorical variables among the three groups (*ALKr, EGFR*-mutated, and wild-type patients) were analyzed by the Fisher exact test. A two-sided *p*-value less than 0.05 was considered significant. Data analysis was performed using R version 3.3.2 (The R Foundation) software.

Results

Patient characteristics and clinical course. Among the three patients with *ALKr* who received both WBRT and ALK-TKI, one lacked detailed medical records of acute AE after WBRT. As a result, only two of these patients were assessed. Twelve patients with *EGFR* mutation were treated with radiotherapy and EGFR-TKI concurrently, and 11 of these patients were eligible for the analysis. With regard to the patients with wild-type disease, 18 were eligible who received WBRT. The patient characteristics are summarized in Table I.

The two female patients with *ALKr*, referred to as patient 1 and patient 2, were 43 and 51 years old, respectively. Both had an Eastern Cooperative Oncology Group performance status of 1 and had no smoking history. Both were without BMs at initial diagnosis; however, they were subject to the emergence of multiple BMs, all of which were asymptomatic, non-measurable lesions, before ALK-TKI was initiated. The initial treatment for BMs was crizotinib for patient 1 and cytotoxic agents for patient 2. After intracranial progression under the use of crizotinib, patient 1 received WBRT of 30 Gy in 10 fractions concurrently with the continuation of crizotinib. In patient 2, rapid aggravation of BMs was observed in a short period, although crizotinib was initiated instead of cytotoxic agents, so ALK-TKI was switched to alectinib. However, this did not control the BMs, and WBRT of 40 Gy in 20 fractions was eventually performed, along with the continuation of alectinib. Patient 1 was alive at the end of the follow-up, and durable efficacy of alectinib was observed, with the BMs controlled after progression under the use of crizotinib. Patient 2 suffered from the progression of BMs under the use of alectinib and ceritinib followed by nivolumab, and finally died. The OS and IPFS were 57.4 and 25.8 months for patient 1, and 26 and 2.3 months for patient 2, respectively.

Acute AEs under concurrent administration of WBRT and ALK-TKI. The two eligible patients with ALKr did not suffer from radiation dermatitis or hematotoxicity of grade2 or more. As for ototoxicity, the unexpected occurrence of grade 3 *otitis media* was confirmed in both patients, and grade 2 otitis externa was confirmed in patient 1 (Table II). Both patients consequently required not only antibiotics but myringotomy and tympanostomy. Both had no definite history of a prescribed medication causing ototoxicity previously. In patient 2, it took 1.2 months from the date of the initial diagnosis to the improvement of the symptoms of *otitis media*; however, it took no less than 4.7 months in patient 1. Meanwhile, the other *ALKr* patient, who received concurrent WBRT and ALK-TKI and had no clinical record of any acquired acute AE, complained of tinnitus and was examined by an otolaryngologist about 33 months after the end of the WBRT. Consequently, abnormal findings of pure tone audiometry at high frequency and tympanometry

Table I. *Patient characteristics*.

Characteristic	Characteristic	*ALKr* (n=2)	*EGFR*-mutated (n=11)	Wild-type (n=18)	*p*-Value
Age, years	Median (range)	47 (43-51)	70 (62-77)	68.5 (38-76)	0.0064*
Gender, n	Male	0	6	9	0.62
	Female	2	5	9	
ECOG-PS, n	0-1	2	7	9	0.54
	2-4	0	4	9	
Smoking history, n	+	0	6	9	0.62
	−	2	5	9	
Number of BMs, n	≤3	0	2	6	0.82
	>3	2	9	12	
Size of largest BMs, n	<1 cm	2	5	4	0.068
	≥1 cm	0	6	14	
Symptom from BMs, n	+	2	6	6	0.15
	−	0	5	12	
Leptomeningeal dissemination, n	+	0	2	0	0.25
	−	2	9	18	
Extracranial metastasis at time of BMs diagnosis, n	+	2	10	13	0.59
	−	0	1	5	
Staging at initial diagnosis, n	I-III	2	1	1	0.013
	IV	0	10	17	
BMs at time of diagnosis, n	+	0	3	6	>0.99
	−	2	8	12	
BMs diagnosis after TKI initiation	+	0	8	0	<0.01
	−	2	3	18	
Initial treatment for BMs, n	Radiotherapy	0	0	14	<0.01
	TKI	1	0	0	
	Radiotherapy + TKI	0	10	0	
	cytotoxic agents	1	1	3	
	surgery	0	0	1	
Radiotherapy method, n	WBRT only	2	9	12	0.82
	WBRT and STI	0	2	6	
Dose/fraction of WBRT, n	30 Gy/10 Fr	1	10	14	0.11
	35 Gy/14 Fr	0	1	4	
	40 Gy/20 Fr	1	0	0	

*For <60 vs. ≥60 years old among the three groups. *ALKr*: Anaplastic lymphoma kinase-rearranged; BMs: brain metastases; ECOG-PS: Eastern Cooperative Oncology Group performance status; *EGFR*: epidermal growth factor receptor; TKI: tyrosine kinase inhibitor; RT: radiotherapy; STI: stereotactic irradiation; WBRT: whole-brain radiotherapy.

indicating ipsilateral sensorineural hearing loss with an unknown cause were confirmed and diagnosed as idiopathic sudden sensorineural hearing loss. The patient received oral corticosteroids and improvement of the hearing loss was finally confirmed at one month after the diagnosis. In patients with *EGFR* mutation and those with wild-type disease, grade 2 *otitis media* was observed in one patients each. Otitis media of grade 2 or more was more frequently observed in patients with *ALKr* compared with those with *EGFR* mutation and those with wild-type disease (p=0.013).

Leukopenia and anemia of grade 2 or more was observed in one and two patients, respectively, and no severe radiation dermatitis was observed in those with *EGFR* mutation. In those with wild-type disease, one patient suffered from grade 2 radiation dermatitis, leukopenia, and thrombocytopenia, and four patients suffered from confirmed grade 2 anemia.

Discussion

There is no recommendation in the current guidelines and no evidence regarding the concurrent administration of cranial radiotherapy and ALK-TKI (20). In our study, both of the patients who concurrently underwent WBRT with ALK-TKI suffered from grade 3 *otitis media* as a consequence of the concurrent treatment. Although the high incidence of ototoxicity might be a result of chance, to our knowledge, there has been no report showing the exacerbation of ototoxicity under the combination of WBRT and ALK-TKI. There has also been no description of *otitis media* as an AE in the clinical trials concerning ALK-TKI (4). Although no definite cause of ototoxicity has been declared, we discuss several possible risk factors for radiation-induced acute *otitis media* in the present study.

Table II. *Summary of the adverse events.*

Adverse event		Grade	*ALKr* (n=2)	*EGFR*-mutated (n=11)	Wild-type (n=18)	*p*-Value*
Dermatitis		2	0 (0)	0 (0)	1 (5)	>0.99
		≥3	0 (0)	0 (0)	0 (0)	
Hematotoxicity	Leukopenia	2	0 (0)	1 (9)	1 (5)	>0.99
		≥3	0 (0)	0 (0)	0 (0)	
	Anemia	2	0 (0)	2 (18)	4 (22)	>0.99
		≥3	0 (0)	0 (0)	0 (0)	
	Thrombocytopenia	2	0 (0)	0 (0)	1 (5)	>0.99
		≥3	0 (0)	0 (0)	0 (0)	
Ototoxicity	Otitis externa	2	1 (50)	0 (0)	1 (5)	0.13
		≥3	0 (0)	0 (0)	0 (0)	
	Otitis media	2	0 (0)	1 (9)	1 (5)	0.013
		≥3	2 (100)	0 (0)	0 (0)	

*For differences in adverse events (grade ≥2) among the three groups. *ALKr*: Anaplastic lymphoma kinase-rearranged; *EGFR*: epidermal growth factor receptor.

In patient 1, the total dose of WBRT was 40 Gy in 20 fractions, which was higher than the dose for the other patients. The reported TD tolerance dose of a 50% probability of complications within 5 years for acute reactions of the middle ear has been estimated to be 40 Gy (21). One study reported that radiation-induced *otitis media* with effusion may decrease when the dose to the middle ear cavity is less than 34 Gy in the treatment of nasopharyngeal carcinoma using the intensity-modulated radiotherapy technique (21). Grade 4 leucopenia also occurred 2 months after the end of WBRT in this patient and might be a risk factor, although it was mainly caused not by WBRT but by the continuation of crizotinib use. In addition, this patient had a comorbidity of chronic sinusitis, which was also worsened by the concurrent therapy. Chronic rhinosinusitis is known to be a predisposing condition for *otitis media* (23). In both patients 1 and 2, corticosteroids were administered for the prevention of cerebral edema, and that might have been a risk factor for infection.

In the treatment of WBRT for BM, a randomized phase III trial demonstrated that acute otitis developed in 5% of patients, including 1% who required the help of an otolaryngologist (24). In *EGFR*-mutated NSCLC, grade 3 *otitis media* is diagnosed in 5% of patients treated with WBRT during the course of concurrent EGFR-TKI use (25). Damage to the eustachian tube, *tensor veli palatini* muscle, cartilage, or nerves by radiotherapy, and direct radiation damage leading to noninfectious inflammation contributed to *otitis media* with effusion (26). In our study, the frequent occurrence of grade 3 *otitis media* might have been due to both ALK-TKI and WBRT exacerbating noninfectious inflammation and mucosal damage in the ET and middle ear cavity. Because decreased morbidity from *otitis media* with effusion was observed when the dosage over the middle ear cavity and the isthmus of the ET was reduced (27), WBRT with a reduced dose over the middle ear and ET with the IMRT technique might also lower the risk of ototoxicity. In addition, one report described that patients with *ALKr* lung cancer suffered from severe mucositis of hypopharyngeal and upper esophageal ulceration after palliative radiotherapy of 30 Gy/10 fractions for metastasis of the cervical spine concurrent with crizotinib (28). It has been speculated that ALK-TKI concurrent with radiotherapy might enhance radiosensitivity and worsen mucositis, based partly on preclinical data suggesting that ALK-TKI enhanced sensitivity to radiation and that ALK-TKI infiltrated into the brain tissue in patients with *ALKr* NSCLC (13, 14). Further investigation is necessary to determine the relationship between the exacerbation of ototoxicity and concurrent therapy in *ALKr* NSCLC.

As for the other acute AEs, no severe dermatitis or hematotoxicity was observed in response to the combination of WBRT and ALK-TKI. In *EGFR*-mutated NSCLC, a meta-analysis demonstrated that patients treated with cranial radiotherapy plus EGFR-TKI experienced rash and dry skin more frequently (4). On the other hand, it has been reported that no significant difference was observed in the incidence of hematotoxicity between patients treated with WBRT plus EGFR-TKI and those treated with WBRT alone (29). Some investigations have consequently reported that concurrent therapy with radiotherapy and EGFR-TKI is safe and tolerated, although there is no high-level evidence to support its safety (4). There are no clinical data on *ALKr* NSCLC, therefore further study is warranted to determine whether or not the combination of radiotherapy and ALK-TKI is tolerable, appropriate, and recommended with respect to the incidence of acute AEs.

In addition, the other *ALKr* patient, who received concurrent treatment with WBRT and ALK-TKI without a clinical record of acute AE, was subject to hearing loss and was finally diagnosed with idiopathic sudden sensorineural hearing loss more than 2 years after the completion of WBRT. It was considered that there might be some relationship between the incidence of hearing loss and the combination of WBRT and ALK-TKI. Sensorineural hearing loss is one of the serious complications of the inner ear induced by radiation, which occurs 1.5-5 years after radiotherapy and is irreversible (30).

In summary, our data suggest that severe ear toxicity was frequently experienced in association with concurrent treatment with WBRT and ALK-TKI without other acute AEs. This investigation is the first to report the acute AEs of radiation dermatitis, hematotoxicity, and ototoxicity in association with combined treatment using WBRT and ALK-TKI. Unexpected severe ear toxicity should be kept in mind when combination therapy involving WBRT and ALK-TKI is administered for BMs. Further investigations in much larger populations are warranted to confirm whether or not the AEs induced by this concurrent therapy are tolerable.

Conflicts of Interest

No competing financial interests exist.

Authors' Contributions

Study concepts: T. Nakashima; Data collection: T. Nakashima; Patient management: T. Nakashima, T. Nonoshita, K. I., and A. N.; Data analysis and interpretation of results: T. Nakashima, T. Nonoshita, and H. H.; Statistical analysis: H. H.; Manuscript writing: T. Nakashima; Manuscript reviewing: H. H., T. Y., K. A., and Y. S.; Supervising the study; Y. S.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (grant numbers: 18K07718).

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Received September 6, 2019
Revised October 4, 2019
Accepted October 11, 2019