Case Summaries of Interstitial Lung Disease reported in Japan

Case 1: Mortatlity case

Patient Background	Occurrence of side effects, Progress of symptoms	
Female, 50s Reason for use: Right breast cancer Stage IV (T4cN3M1) : Metastasis (bone, lung, pleura contralateral breast) Abemaciclib (name of drug) Daily dose: 300mg (150 mg, twice daily)		Complications: Congenital hearing disorder with speech impairment, Headache Familial history : Deafness in the relatives, Family configuration: husband (Deafness), Niece (Nurse) Anamnestic history: Thromboembolism, No history of radiation therapy, smoking, surgery and allergy History of prior treatment: Injection of Fulvestrant as an initial therapy Oral administration of Exemestane tablets and Everolimus tablets as a secondary therapy. No respiratory or other symptoms suggestive of suspected interstitial lung disease were observed. Oral administration of Exemestane tablets and Palbociclib capsules as a tertiary therapy. Oral administration of Palbociclib capsules and injection of Fulvestrant as a quartic therapy Concomitant drugs: Denosumab (genetical recombination), Oxycodone hydrochloride hydrate, Loxoprofen sodium hydrate, Amlodipine besilate, Sennoside tablets, Esomeprazole magnesium hydrate, Calcium lactate hydrate
	231 days before administration	PET/CT scan revealed lesions in the mammary gland and bilateral axillary nodes. No observed finding of suspected interstitial lung disease.
	91 days before administration	No findings of suspected interstitial lung disease were observed by chest X-ray.
	Day 1 of administration	With a trend toward gradual increase in tumor maker, treatment regimen was switched to Abemaciclib 150 mg twice daily and injection of Fulvestrant. No respiratory symptoms such as cough or sputum were observed.
	28 days after administration	Administration of Fulvestrant injection, Denosumab (genetical recombination) injection, Oxycodone hydrochloride hydrate
	34 days after administration (the day of termination)	The patient complained of increase in inveterate headache to family members, but did not visit the doctor. The patient did not take Abemaciclib.
	35 days after administration	Lack of appetite and the patient slept whole day without visiting the doctor. Presence or absence of respiratory symptoms such as cough was unknown.
	36 days after administration	The patient slept whole day. Communicated with family member as usual until 21:00. No one in her close circle had any symptoms suggestive of suspected infection. Presence or absence of pyrexia was unknown.
	<u>37 days after administration</u> <u>(the day of onset)</u>	7:10 Emergency corps requested because the patient became violent and fainted in agony in her own room. The patient was too violent to have her blood pressure measured at home. 7:57 Emergency corps arrived. SpO_2 64%, Japan Coma Scale (JCS) III-200, Body temperature 38.0 Celsius degree, respiratory rate 40/min Blood pressure was 160/80 mmHg in the ambulance car and gradually decreased thereafter. 8:24 Arrival at the hospital, positive for decerebration stiffness and right concomitant deviation, negative for light reflex tests. Blood gas examination: PaO_2 84 mmHg, $PaCO_2$ 34 mmHg Head CT scan: No bleeding and no obvious metastasis were observed, diffused brain oedema was observed. 12-lead Electrocardiogram and transthoracic echocardiography: Acute myocardial infarction and arrhythmia were denied. 9:00 Tracheal cannulation conducted and artificial respiration started. Chest X-ray: infiltrative opacity in right mid-lung area and bilateral lower lung area were observed. Contrast enhanced CT: Lymph nodes were not enlarged. Wide spread consolidation in the bilateral lower lung area surrounded by ground glass opacity observed. It looked like pneumonia however, diagnosed as acute respiratory distress syndrome (ARDS) based on its distribution. Negative for pulmonary embolism. Negative for sputum culture, blood culture and influenza test. KL-6 1425 U/mL (Reference value: < 500 U/mL), SP-D 556 ng/mL, SP-A 163.8 ng/mL Test for RS virus, mycoplasma, Streptococcus pneumonia and Legionella urinary antigen, beta-D glucan and bronchoalveolar lavage were not conducted. Based on observation shown above, the patient diagnosed with interstitial lung disease, ARDS and hypoxic encephalopathy (brain-dead) caused by respiratory failure. Administration of methylprednisolone sodium succinate for interstitial lung disease and concentrated Glycerol and fructose for hypoxic encephalopathy started.
	1 day after onset	No cells in cerebral spinal fluid. Negative for cerebral spinal fluid cytological diagnosis. JCS III-300
	2 days after onset	Administration of methylprednisolone sodium succinate and concentrated Glycerol and fructose terminated.
	7 days after onset	3:10 Cardiac arrest, death caused by interstitial lung disease and hypoxic encephalopathy. Autopsy not conducted.

Laboratory test values

Test item	Reference value	Unit	14 days before administration	Day of start administration	14 days after administration	28 days after administration	<u>37 days after administration (the day of onset)</u>	1 day after onset

LDH	106-211	IU/L	216	217		238	613	618
CRP	0.00-0.30	mg/dL	0.08	0.33		0.10	13.45	8.51
WBC	4000-9000	/uL	3600	3400		4100	10900	5700
Neut	40.0-71.9	%	59.7	57.3		68.9	94.2	91.7
PT-INR	0.84-1.29		0.89	0.94		0.96	1.12	1.22
ALT	4-44	IU/L				13		
FDP	0.0-5.0	ug/ml					20.1	123.0
CA15-3		U/ml	36.6		32.2			

Case 2: Recovered case

Patient Background	Occurrence of side effects, Progress of symptoms	
Female, 70s Reason for use: Right breast cancer with pleural dissemination Abemaciclib (name of drug) Daily dose: 300mg (150 mg, twice daily) then reduced to 200 mg (100 mg, twice daily)		History of prior treatment: Approximately 20 years before administration of Abemaciclib: Neoadjuvant chemotherapy (no detailed information), breast-conserving surgery was conducted for right breast cancer (Stage IIB), radiation therapy for conserved right breast (chest 60 Gy) were conducted. Approximately 16 years before administration of Abemaciclib: Treatment by anastrozole tablets were started (Unknown whether this as a 1st line therapy or not). Approximately 15 years before administration of Abemaciclib: Capecitabine tablets were administered. Approximately 13 years before administration of Abemaciclib: Lumber resection (metastasis of breast cancer) Approximately 7 years before administration of Abemaciclib: Uterus and ovary resection (metastasis of breast cancer) Approximately 2 years before administration of Abemaciclib: Fulvestrant injection were administered. Approximately 1 year before administration of Abemaciclib: Eribulin mesilate product were administered. Bevacizumab (genetical recombination) injection were started in summer of that year. Approximately 4 months before administration of Abemaciclib: Letrozole tablets and Palbociclib capsule were administered. Concomitant drugs: Famotidine, Gosha - jinki - gan, Hange-shashin-to, pregabalin, furosemide tablets, polaprezinc
	7 days before administration	CT scan observation of lung area were normal. No respiratory symptoms such as cough and dyspnea.
	The day of start administration	Stomatitis was observed during the treatment by letrozole tablets and palbociclib capsules. Administration of Abemaciclib 150 mg twice daily and letrozole tablets started for breast cancer. At the time of start of Abemaciclib PS was 0.
	14 days after administration	Creatinine increased and hypercalcemia (non serious) occurred. Abemaciclib was discontinued.
	25 days after administration	After recovery from creatinine increase and hypercalcaemia, administration of Abemaciclib at reduced dose of 100 mg, twice daily restarted.
	51 days after administration	CT: Reduction of pleural effusion observed, interstitial shadow in the lung area was not observed, pleural dissemination reduced, tumor marker decreased (detailed test values were not available) , no respiratory symptoms.
	97 days after administration	Body temperature 38.5 Celsius degree
	104 days after administration	Body temperature was 38s Celsius degree and returned to normal. Patient's symptoms were monitored. No respiratory symptoms such as cough were noted.
	110 days after administration	Patient felt dyspnea from the morning, which exacerbated in the late afternoon. She visited the emergency department at night.
	(the day of onset)	Body temperature 37 Celsius degree, PaO_2 58.3mmHg. By oxygen inhalation (reservoir mask 10 L/min, mechanical ventilator was not used) SpO_2 in the 90% range wasmaintained. Ground glass opacity was observed in the bilateral upper lobes, lower lobe, right middle lobe of the lung by CT scan. Sputum culture and mycoplasma antigen examination were negative. Influenza test, cytomegalovirus antigen examination, drug induced lymphocyte stimulation test, bronchoalveolar lavage and biopsy were not conducted. Patient was diagnosed with interstitial lung disease (drug induced pneumonia) and hospitalized. Abemaciclib was terminated. 3 days of pulse therapy by methylprednisolone sodium succinate 1000 mg/day was conducted from this day. Tazobactam/Piperacillin hydrate 4.5 g, three times per day were administered for 5 days.
	2 days after onset	KL-6 2979 U/mL, beta-D glucan <6.0 pg/mL, SP-D 955.9 ng/mL
	3 days after onset	Pulse administration of steroid for 3 days and then oral steroid administration 60 mg/day was started.
	5 days after onset	Reservoir mask oxygen was 8 L/min.
	6 days after onset	Reservoir mask oxygen was reduced to 6 L/min.
	13 days after onset	Oral steroid was reduced to 40 mg/day.
	20 days after onset	KL-6 2932 U/mL, oxygen inhalation was terminated. Oral steroid was reduced to 30 mg/day.
	28 days after onset	Oral steroid was reduced to 25 mg/day.
	33 days after onset (the day of outcome)	CT: Ground glass opacity almost returned to normal, therefore patient was considered to have recovered from interstitial lung disease. Oral steroid was reduced to 20mg.
	47 days after onset	Due to decreased strength, patient was kept hospitalized and progress of the symptoms was observed. Patient was doing rehabilitation. Patient was able to go outside and stay overnight out of hospital.

Laboratory test values

Test Item	Unit	4 days after onset	6 days after onset	9 days after onset	13 days after onset	16 days after onset	20 days after onset
WBC	uL	8140	7090	6290	9750	8290	8190
Neut	uL	6950	5790	4480	7250	6070	5880
CRP	mg/dL	2.0	1.1	0.32	0.09	0.05	1.52
LDH	IU/L	478	358	368	305	314	286