American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e920809
DOI: 10.12659/AJCR.920809

Received: 2019.10.18
Accepted: 2019.12.03
Available online: 2020.01.24
Published: 2020.02.04

Febrile Neutropenia in a Patient with Non-Small Cell Lung Cancer Treated with the Immune-Checkpoint Inhibitor Nivolumab

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: Kuniaki Shirao has received honoraria from Taiho Pharmaceutical Co., and Bristol-Myers Squibb Co.
Source of support: Kuniaki Shirao has received research funding from Taiho Pharmaceutical Co., Bristol-Myers Squibb Co., Chugai Pharmaceutical Co., Pfizer, Inc., Ono Pharmaceutical Co., Daiichi Sankyo Co., Sanofi K.K., Kyowa Hakko Kirin Co., Astellas Pharma, Inc., Shionogi & Co., and Takeda Pharmaceutical Co.

Patient: Male, 57-year-old
Final Diagnosis: Febrile neutropenia
Symptoms: Fever
Medication: Nivolumab
Clinical Procedure: Chemotherapy
Specialty: Oncology

Objective: Adverse events of drug therapy

Background: Nivolumab is a human IgG4 monoclonal antibody against human programmed cell death 1 (PD-1). It has demonstrated efficacy against metastatic non-small cell lung cancer (NSCLC). Treatment with nivolumab is sometimes associated with immune-related adverse events (ir AEs) in patients. These specific ir AEs include pneumonitis, hypothyroidism, dermatitis, enterocolitis, hepatitis, and neuropathy. However, hematological toxicity is rare.

Case Report: A 57-year-old man with lung adenocarcinoma, with brain and adrenal gland metastases, was therefore started on nivolumab therapy as third-line treatment. After administration of the second dose with nivolumab, grade 3 febrile neutropenia (FN) and grade 2 liver dysfunction developed in the patient. The patient was started to on intravenous antibiotics, granulocyte colony-stimulating factor (G-CSF), and corticosteroids. Neutrophil counts and liver function gradually improved, and corticosteroids were tapered over 6 weeks. However, the patient was re-treated with G-CSF because the neutrophil counts decreased again.

Conclusions: Care needs to be taken with such patients because neutropenia due to treatment with nivolumab can recur, as well as other ir AEs.

MeSH Keywords: Agranulocytosis • Carcinoma, Non-Small-Cell Lung • Febrile Neutropenia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/920809

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Background

Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells, and NK cells. It is an inhibitory molecule that binds to the PD-1 ligand (PD-L1) and PD-L2. PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells, as well as hematopoietic cells. The PD-1: PD-L1/2 interaction directly inhibits apoptosis of the tumor cell, promotes peripheral T effector cell exhaustion, and promotes conversion of T effector cells to Treg cells [1].

Nivolumab is a human IgG4 monoclonal antibody that binds and blocks PD-1 receptors on cancer cell membranes, which results in the release of cancer immune-tolerance. Immune-related adverse events (ir AEs) such as liver damage, dysfunction of internal secretion, enterocolitis, and skin reactions are reported as AEs of nivolumab [2], while hematotoxicity is rare. Here, we present a case of neutropenia showing a biphasic phenomenon in a patient with non-small cell carcinoma due to treatment with nivolumab is presented.

Case Report

A 57-year-old man was diagnosed with lung adenocarcinoma in February 201X. He had both brain and adrenal gland metastases. Molecular tests showed that the genes for epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) were negative. The tumor proportion score was unknown. The patient had a smoking history and pulmonary emphysema.

After cyberknife stereotactic radiosurgery for the brain metastasis, the patient received 2 courses each of cisplatin-pemetrexed chemotherapy and docetaxel therapy. The patient was administered docetaxel on May 6. With both treatments, severe myelosuppression and FN did not occur. However, computed tomography (CT) showed disease progression after 2 cycles of docetaxel therapy. The patient was therefore started on nivolumab therapy (3 mg/kg every 2 weeks) as the third-line treatment on June 1. The patient's absolute neutrophil count (ANC) at that time was normal (6150/μL).

The first and second doses with nivolumab were well tolerated, and the patient did not complain of any potential AEs. At the time of the third dose with nivolumab, on day 29 after administration of the first dose with nivolumab, Common Terminology Criteria for Adverse Events (CTCAE) grade 1 liver dysfunction and asymptomatic grade 3 neutropenia (920/μL) were detected. Therefore, the treatment was discontinued. Before nivolumab administration, the patient had been taking famotidine from January 201X. Because it is one of the agents that can cause agranulocytosis, it was stopped and switched to rabeprazole.

On day 32 after the first dose with nivolumab (day 58 after the last dose with docetaxel), the patient developed grade 3 FN, with the following laboratory results: white blood cells (WBC) 1.71 g/L; ANC 980/μL; hemoglobin (Hb) 8.1 g/L; platelets (PLT) 21.2×10^4/μL; aspartate aminotransferase (AST) 166 IU/L; alanine aminotransferase (ALT) 169 IU/L; and C-reactive protein (CRP) 12.5 mg/L (Table 1). The patient's temperature was 39.0°C.

Because it was thought that the neutrophil count was likely to decrease further, the patient was diagnosed with FN. The tumor was significantly reduced, and there was no appreciable source of infection on CT (Figure 1). After blood cultures were taken, the patient was started on intravenous antibiotics.

On July 7 (day 37), a bone marrow biopsy was performed because the ANC had decreased to 280/μL and Ferritin had

Table 1. Blood test results.

	5/27 (day –5*)	6/15 (day 15*)	6/29 (day 29*)	7/2 (day 32*)	7/7 (day 37*)	7/9 (day 42*)
WBC (/μl)	8630	4740	1640	1710	760	4440
ANC (/μl)	6150	3590	920	980	280	3500
Hb (g/dl)	8.9	8.1	8.1	7.2	8.7	8.0
Plt (104/μl)	29.1	23.1	21.2	17.1	21.3	16.6
CRP (mg/dl)	5.3	14.1	7.4	12.5	6.48	5.43
AST (U/L)	9	14	67	166	208	178
ALT (U/L)	6	11	69	169	213	233

* Days after administration of the first nivolumab dose. WBC – white blood cells; ANC – absolute neutrophil count; Hb – hemoglobin; Plt – platelets; CRP – C-reactive protein; AST – aspartate aminotransferase; ALT – alanine aminotransferase.

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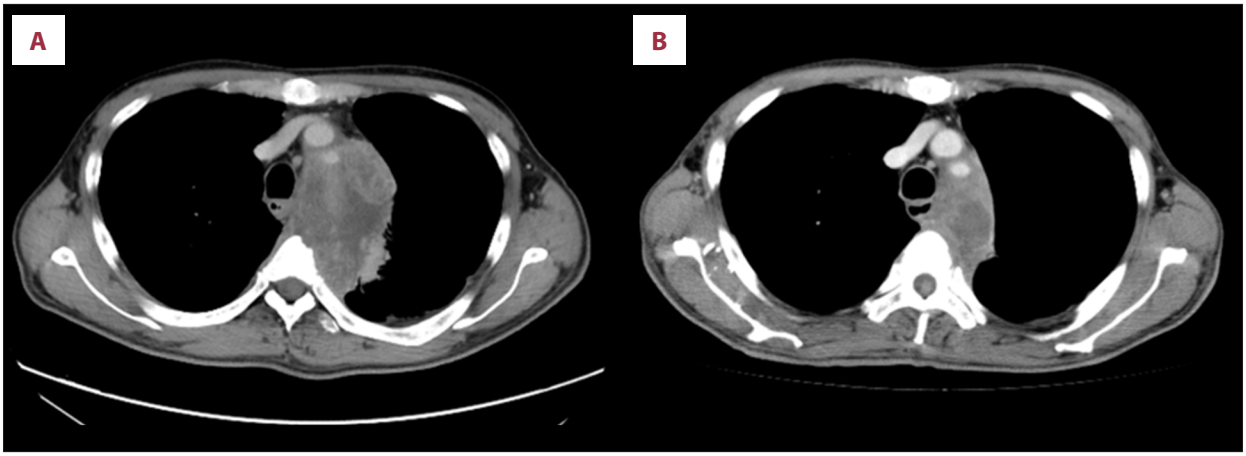

Figure 1. CT images. Lung adenocarcinoma is present in the mediastinum from the left upper lobe before nivolumab treatment in May 201X (**A**). Hospitalization for FN on day 32 after administration of the first dose with nivolumab. The tumor is significantly reduced with no appreciable source of infection on CT (**B**).

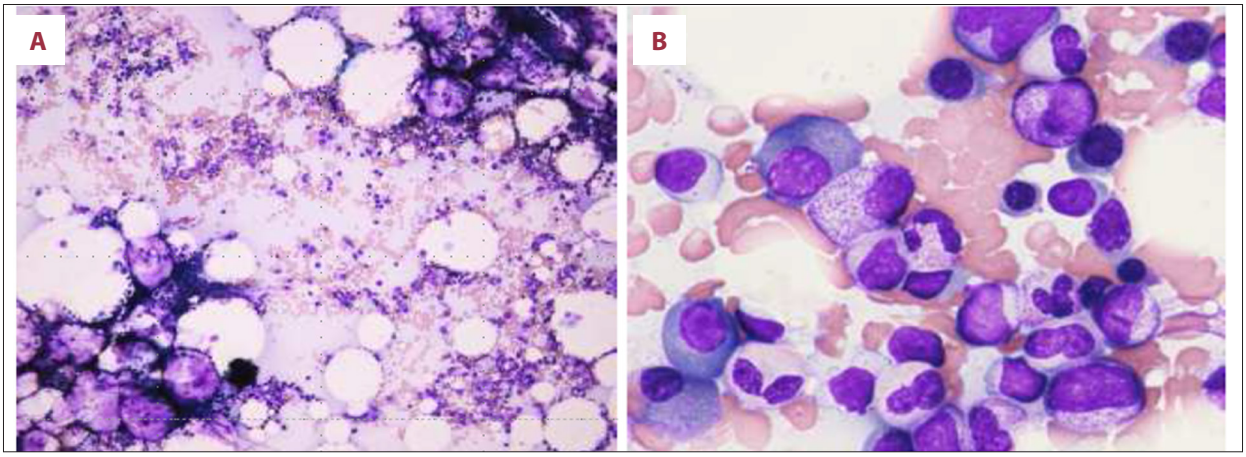

Figure 2. Bone marrow imaging. (**A:** ×100), (**B:** ×400). There is no malignant tumor invasion into the bone marrow. The specimen shows agranulocytosis.

increased to 1732 ng/ml. Malignant tumor infiltration to bone marrow was not present. The biopsy specimen showed agranulocytosis (Figure 2) and the bone marrow examination results are shown in Table 2. The mononuclear phagocyte system constitutes approximately 1.0%.

Antineutrophil antibodies that induce neutropenia were not detected in the patient's serum. On day 32, grade 2 liver dysfunction (ALT 166 IU/L; AST 169 IU/L) was also detected. The patient was started on treatment with granulocyte G-CSF for 4 days for neutropenia and prednisolone 0.5 mg/kg/day for liver dysfunction. With the withdrawal of nivolumab therapy and the administration of G-CSF, the neutrophils increased. However, on July 14 (day 44), methylprednisolone was administered at a dose of 2 mg/kg (125 mg/day) because the liver function test results worsened (ALT 191 IU/L; AST 307 IU/L). Liver function then gradually improved, and corticosteroids were tapered over 6 weeks.

The patient was re-treated with G-CSF because only the neutrophil counts decreased again (ANC 500/μL) on August 16 (day 77). ANC immediately normalized, and liver dysfunction did not recur (Figure 3). The patient was then diagnosed with widespread disease progression and received palliative treatment.

Discussion

The course of this patient demonstrates 2 important clinical points. FN due to nivolumab was present, along with the recurrence of neutropenia due to nivolumab. Treatment with nivolumab is sometimes associated with ir AEs in patients. These specific ir AEs include pneumonitis, hypothyroidism, dermatitis, enterocolitis, hepatitis, and neuropathy. However, hematological toxicity is rare. A recent study on immune-checkpoint inhibitors (ICIs)-related hematological toxicity reported that anemia and thrombocytopenia are the most common

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Table 2. bone marrow examination.

NCC (/mm³)	3.3×10⁴	Basophil	0.6
MgK (/mm³)	47	Monocyte	2.0
M/E ratio	1.57	Total erythroid (%)	35.2
Total myeloid (%)	55.4	Pro-erythroid	0.2
Blast	1.6	Mega	3.6
Promyelocyte	6.0	Macro	0
Myelocyte	20.2	Normal	31.4
Metamyelocyte	13.2	Lymphocytes (%)	4.8
Stab cell	7.8	Plasma cell (%)	3.6
Seg	3.8	Phagocytes (%)	1.0
Eosinophil	0.2	Tumor cell invasion	–

NCC – nucleated cell; MgK – megakaryocyte; M/E ratio – myeloid erythroid ratio.

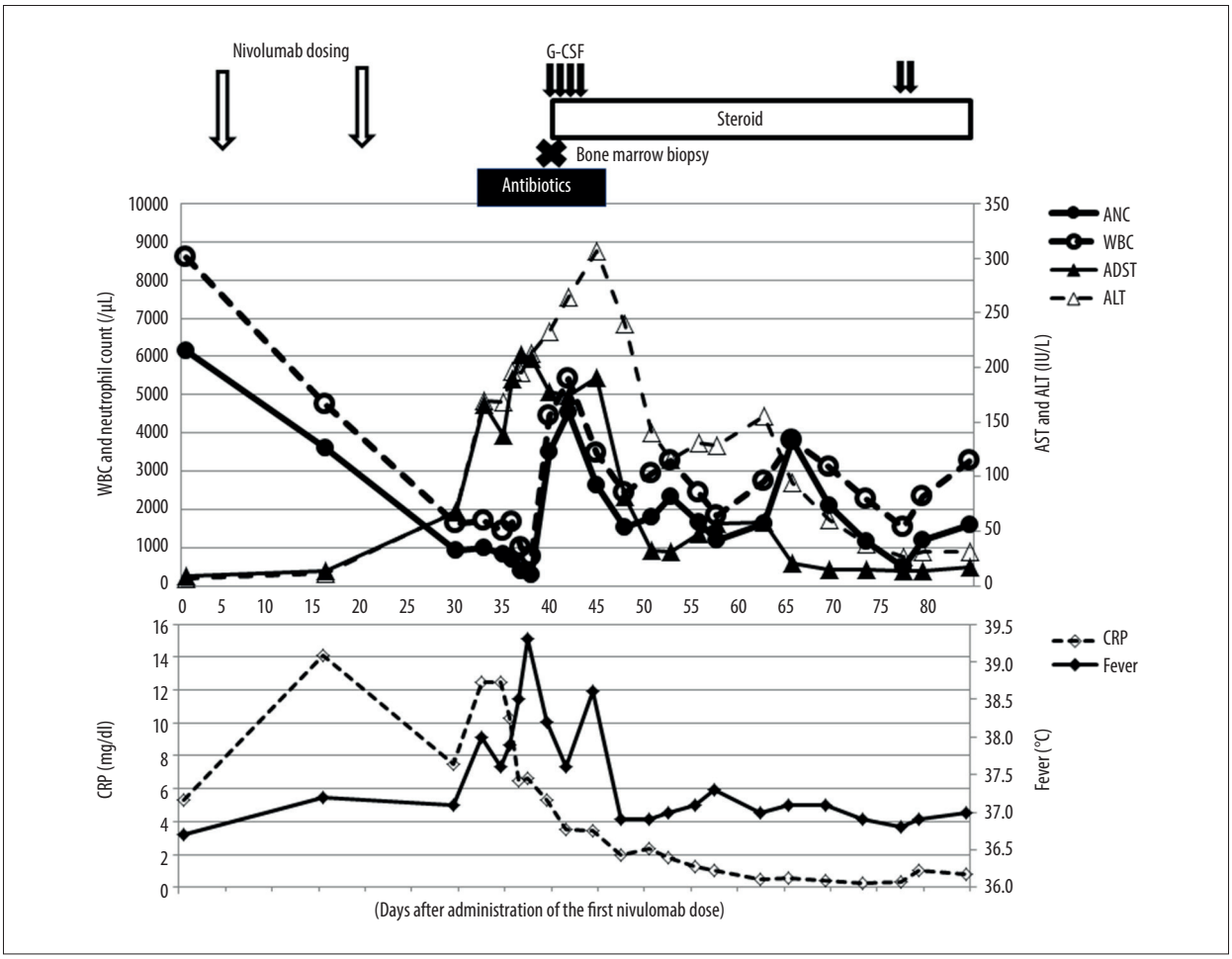

Figure 3. Timeline for white blood cell count (WBC), absolute neutrophil count (ANC), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels since nivolumab dosing.

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hematological toxicities [3]. The incidence of anemia, thrombocytopenia, and neutropenia was 9.8%, 2.8%, and 0.94%, respectively [4]. The rate of nivolumab-related neutropenia is 0–0.6% in NSCLC [5–7].

According to the European Society of Medical Oncology (ESMO) guidelines, FN is defined as an oral temperature >38.5°C or 2 consecutive readings of >38.0°C for 2 h and an ANC <500/μL, or expected to fall below 500/μL. Therefore, the present patient was diagnosed with FN. In 11% of patients with hematological malignancies and 5% of patients with solid tumors, FN results in death due to infectious complications [8].

There have been 3 reported cases of neutropenia or agranulocytosis with NSCLC treated with nivolumab. Tabchi et al. [9] reported severe agranulocytosis due to nivolumab therapy; the patient's past medical history included ulcerative colitis and lumpectomy for breast cancer, and she had severe agranulocytosis and liver dysfunction after 2 courses of nivolumab therapy for NSCLC. Turgeman et al. [10] reported 2 cases of neutropenia due to nivolumab therapy; 1 patient had a past history of Crohn's disease, and after 5 courses of nivolumab therapy, she had neutropenia and diarrhea due to a Crohn's exacerbation. Another patient had a history of intermediate-grade follicular lymphoma that had been treated with rituximab. He had grade 4 neutropenia. None of these 3 cases was diagnosed with FN.

There are various causes of neutropenia in cancer patients. It may be associated with the cytotoxic effects of chemotherapy or radiotherapy, systemic infections, some concomitant drugs, and bone marrow metastases.

On day 15, CRP was elevated (14.1 mg/dl). Neither fever nor malaise was recognized as the symptom of virus infection, and the cause of the clear CRP increase was unknown.

In this case, the patient had no history of malignancy except for NSCLC and had no autoimmune disease. Bone scintigraphy was not performed, but the bone marrow examination showed no bone marrow infiltration of cancer. Therefore, it was not considered to be the cause of neutropenia. Neutropenia caused by systemic infections before the administration of nivolumab was ruled out. Prior to nivolumab administration, he started famotidine, loxoprofen, oxycodone, and magnesium oxide in January 201X, rabeprazole on June 29, and trimethoprim-sulfamethoxazole at a dose of 1 g on July 14 to November 2 for the prevention of Pneumocystis pneumonia. Except for famotidine, he continued to take the other drugs throughout the entire treatment for FN and hepatitis after the improvement of recurrent neutropenia on day 77. Therefore, the FN was likely caused by nivolumab or famotidine. Certainly, famotidine is one of the agents causing agranulocytosis [11]. However, most cases of severe neutropenia or agranulocytosis present within the first 60 days after beginning the offending drug [12,13]. It is difficult to conclude that the febrile neutropenia in the present case was caused by famotidine; therefore, the neutropenia was probably caused by nivolumab. There are 2 developmental mechanisms of agranulocytosis caused by some concomitant medications [14]. One is an immunologic mechanism that causes the production of the antineutrophil antibody. The other direct mechanism is thought to involve drugs or their metabolites binding to the intranuclear material of granulocytic series progenitor cells and intracytoplasmic protein. The latter mechanism is most likely, because antineutrophil antibodies were not detected in the present case.

After G-CSF administration for recurrent neutropenia on August 16 (day 77), liver function had not deteriorated. Therefore, G-CSF was unlikely to be the cause of liver damage. Liver function deteriorated despite administration of prednisolone 0.5 mg/kg/day on July 14 (day 44), but improved after increasing the dose of methylprednisolone to 2 mg/kg (125 mg/day).

Drug-induced neutropenia usually resolves within 1–3 weeks after cessation of the offending drug, whereas the present patient experienced recurrent only neutropenia without liver dysfunction on day 77 and was treated again with G-CSF. There are some reports that pneumonitis associated with ICIs recurred during drug withholding/corticosteroid therapy after initial clinical improvement [15,16]. Similarly, Naqash et al. reported isolated neutropenia associated with PD-1 antibody in a patient who relapsed [17]. Although the detailed mechanisms of this unusual phenomenon remain to be investigated, it may be that durable responses have been CD8+ linked to ICI-induced persistent T effector memory fraction against tumor cells [18]. The possible cross-reactivity of these T cells against normal cells after stopping treatment may be of the plausible mechanisms that have been suggested to contribute to this phenomenon [19]. Although there are reports of neutropenia due to anti-PD-1 antibody administration, it is important to show that neutropenia alone may recur when the patient has different ir AEs.

Conclusions

A case of FN occurring in an NSCLC patient treated with nivolumab was described. One should be careful in such cases because the neutropenia due to nivolumab may recur, as well as other ir AEs.

Conflict of interests

Kuniaki Shirao has received honoraria from Taiho Pharmaceutical Co., and Bristol-Myers Squibb Co.

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References:

1. Francisco LM, Salinas VH, Brown KE et al: PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med, 2009; 206: 3015–29
2. Pennock GK, Chow LQ: The evolving role of immune checkpoint inhibitors in cancer treatment. Oncologist, 2015; 20: 812–22
3. Davis EJ, Salem JE, Young A et al: Hematologic complications of immune checkpoint inhibitors. Oncologist, 2019; 24: 584–88
4. Petrelli F, Ardito R, Borgonovo K et al: Haematological toxicities with immunotherapy in patients with cancer: A systematic review and meta-analysis. Eur J Cancer, 2018; 103: 7–16
5. Borghaei H, Paz-Ares L, Horn L et al: Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. N Engl J Med, 2015; 373: 1627–39
6. Brahmer J, Reckamp KL, Baas P et al: Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med, 2015; 373: 123–35
7. Carbone DP, Reck M, Paz-Ares L et al: First-line nivolumab in Stage IV or recurrent non-small-cell lung cancer. N Engl J Med, 2017; 376: 2415–26
8. de Naurois J, Novitzky-Basso I, Gill MJ et al: Management of febrile neutropenia: ESMO Clinical Practice Guidelines. Ann Oncol, 2010; 21(Suppl, 5): v 252–56
9. Tabchi S, Weng X, Blais NL Severe agranulocytosis in a patient with metastatic non-small-cell lung cancer treated with nivolumab. Lung Cancer, 2016; 99: 123–26
10. Turgeman I, Wollner M, Hassoun G et al: Severe complicated neutropenia in two patients with metastatic non-small-cell lung cancer treated with nivolumab. Anticancer Drugs, 2017; 28: 811–14
11. Aymard JP, Aymard B, Netter P et al: Haematological adverse effects of histamine H2-receptor antagonists. Med Toxicol Adverse Drug Exp, 1988; 3: 430–48
12. Andersohn F, Konzen C, Garbe E: Systematic review: Agranulocytosis induced by nonchemotherapy drugs. Ann Int Med, 2007; 146: 657–65
13. Pontikoglou C, Papadaki HA: Idiosyncratic drug-induced agranulocytosis: The paradigm of deferiprone. Hemoglobin, 2010; 34: 291–304
14. Tesfa D, Keisu M, Palmblad J: Idiosyncratic drug-induced agranulocytosis: Possible mechanisms and management. Am J Hematol, 2009; 84: 428–34
15. Naidoo J, Wang X, Woo KM et al: Pneumonitis in patients treated with anti-programmed death-1/programmed death ligand 1 therapy. J Clin Oncol, 2017; 35: 709–17
16. Tanaka R, Fujisawa Y, Sae I et al: Severe hepatitis arising from ipilimumab administration, following melanoma treatment with nivolumab. Jpn J Clin Oncol, 2017; 47: 175–78
17. Naqash AR, Appah E, Yang LV et al: Isolated neutropenia as a rare but serious adverse event secondary to immune checkpoint inhibition. J Immunother Cancer, 2019; 7: 169
18. Ribas A, Shin DS, Zaretsky J et al: PD-1 blockade expands intratumoral memory T cells. Cancer Immunol Res, 2016; 4: 194–203
19. Young A, Quandt Z, Bluestone JA: The balancing act between cancer immunity and autoimmunity in response to immunotherapy. Cancer Immunol Res, 2018; 6: 1445–52

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