Febrile Neutropenia in a Metastatic Melanoma Patient Treated with Ipilimumab – Case Report

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Established Facts
- Treatment with ipilimumab is linked to the occurrence of immune-related adverse events.
- Febrile neutropenia is a very common adverse event in cancer patients treated with chemotherapy, but during immunotherapy it is rarely observed.

Novel Insights
- Clinicians should be aware that febrile neutropenia may occur in advanced melanoma patients treated with ipilimumab.

Keywords
Ipilimumab · Anti-CTLA4 · Immunotherapy · Melanoma

Summary
Background: Ipilimumab is a fully human monoclonal antibody (mAb) targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4). Ipilimumab is currently approved in the U.S. and Europe for the treatment of metastatic melanoma in the first- and second-line treatment. Treatment with ipilimumab is linked to immune-related adverse events (irAEs) occurring in the majority of patients. These specific AEs include dermatitis, gastrointestinal disorders (diarrhea, colitis), hepatitis, hypophysitis, hypothyroidism, neuropathy, and iritis/inflammation of the ciliary body. Case Report: We report a case of febrile neutropenia with agranulocytosis in the blood smear of a 35-year-old metastatic melanoma patient treated with ipilimumab 3 mg/kg. Conclusion: This AE was probably caused by antineutrophil antibodies associated with ipilimumab treatment. To our knowledge this is the first case report of febrile neutropenia in a metastatic melanoma patient treated with ipilimumab 3 mg/kg.

Introduction
Ipilimumab (Yervoy®, Bristol-Myers Squibb GmbH & Co. KGaA, Munich, Germany) is a fully human monoclonal antibody (mAb) targeting cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 is an immune checkpoint molecule that is up-regulated on activated T-cells, which suppresses further activation of specific CD4+ and CD8+ T-cells by interaction with dendritic cells (DC) or...
directly as a result of a contact between suppressor and effector T lymphocytes. The anti-CTLA4 monoclonal antibody by blocking the interaction of CTLA-4 with CD80/86 switches off the mechanism of immune suppression and enables continuous unrestrained stimulation of T-cells by DC [1]. Ipilimumab is currently approved in the U.S. and Europe for the treatment of metastatic melanoma in first and second lines of treatment.

The efficacy of ipilimumab was improved in 2 phase III studies conducted in advanced (unresectable stage III or IV) melanoma patients. In the MDX010–20 trial patients receiving 3 mg/kg ipilimumab, after failure of earlier systemic therapy, demonstrated longer median overall survival (OS) compared to those treated in the control group with the glycoprotein 100 (gp100) vaccine (10.1 vs. 6.4 months; hazard ratio (HR) = 0.66, p < 0.003) [2]. Another phase III study (CA 184–024) evaluated 10 mg/kg ipilimumab combined with dacarbazine compared to dacarbazine alone in the first-line treatment. The study demonstrated longer median OS in patients receiving ipilimumab with chemotherapy (11.2 vs. 9.1 months; HR = 0.72, p = 0.0009) [3]. A recently presented pooled analysis of long-term survival data from 10 phase II and 2 phase III trials of ipilimumab in advanced melanoma patients demonstrated 11.4-month median OS. 3-year survival was observed in 22% of patients. In these trials with a 10-year median follow-up a plateau in the ipilimumab OS curve was observed beginning at approximately 2–3 years, suggesting long-term survival [4]. However treatment with ipilimumab is associated with development of immune-related adverse events (irAEs) occurring in the majority of patients. The most frequently observed irAEs are dermatitis and gastrointestinal disorders [5]. However to our knowledge episodes of febrile neutropenia induced by low-dose (3 mg/kg) ipilimumab have not been described in the literature. To date only Akhtari et al. [6] have published a case report on a patient developing autoimmune thrombocytopenia and neutropenia with concomitant fever following administration of high-dose ipilimumab (10 mg/kg), a dose which is not currently approved for the treatment of metastatic melanoma patients.

Case Report

In September 2010, a 35-year-old man underwent resection of primary nodular ulcerated melanoma (Breslow 4 mm) located on an upper limb. The sentinel node biopsy revealed metastatic cells in 1 of 2 axillary lymph nodes resected. The patient underwent subsequent resection of in-transit metastases, and axillary lymph node dissection which was negative for further metastatic lymph nodes. In 04/2011, positron emission tomography-computed tomography (PET-CT) examination demonstrated dissemination of melanoma to the right axillary lymph nodes, subcutaneous tissue, lungs, liver, bones, and left suprarenal gland. The patient was administered 2 cycles of chemotherapy based on dacarbazine (1,000 mg/m² q2w) due to symptomatic disease progression (brain metastases). Following whole brain irradiation the patient was enrolled (08/2011) in the Patients Assistance Program (Ipilimumab Expanded Access Program) conducted in the Department of Cancer Immunology at Greater Poland Cancer Center, Poznan, Poland. All peripheral blood counts were within the normal laboratory range at the beginning of ipilimumab treatment. The patient was administered 3 cycles of ipilimumab 3 mg/kg every 3 weeks. At that time he was not taking any other medications. Following 3 doses of ipilimumab the patient developed progression of the disease in the right axillary lymph nodes, subcutaneous tissue, lungs, liver, bones, and suprarenal glands. Intracranial metastases were stable.

On day 14 after administration of the 3rd ipilimumab dose the patient developed febrile neutropenia with the following laboratory results: white blood cells (WBC) 1.63 g/l; neutrophils (absolute neutrophil count, ANC), basophils, and eosinophils - undetectable; platelets (PLT) 256 G/l; hemoglobin (Hgb) 7.6 mmol/l, C-reactive protein (CRP) 111.7 mg/l. The peripheral leucocyte blood smear demonstrated solely lymphocytes (75%), monocytes (25%), and single blasts. The patient’s body temperature exceeded 39°C, and he presented with cough and rash. Common Terminology Criteria for Adverse Events (CTCAE) grade 1. Chest X-ray did not demonstrate any abnormalities. He started oral antibiotic and antifungal treatment (amoxicillin with clavulanic acid and fluconazole). After 8 days no improvement in the management of febrile neutropenia was observed. The laboratory results were as follows: WBC 1.54 g/l; ANC, basophils, and eosinophils - undetectable; Hgb 7.4 mmol/l; PLT 479 g/l; CRP 81.5 mg/l. The peripheral leucocyte blood smear demonstrated only lymphocytes (73%) and monocytes (27%) and single blasts. The blood and urine cultures were negative for bacteremia. The patient was given 48 m units of filgrastim subcutaneously, meropenem intravenously (i.v.), fluconazole i.v., and 2 mg/kg of methylprednisolone (120 mg) i.v. daily.

After an additional 8 days (16 days from the onset of febrile neutropenia) the laboratory results showed improvement: WBC 4.33 g/l; ANC 1.0 g/l; basophils 0.02 g/l; eosinophils 0.01 g/l; Hgb 6.8 mmol/l; PLT 328 g/l; CRP 30.3 mg/l. The peripheral leucocyte blood smear demonstrated lymphocytes (79%) and monocytes (13%), clubbed neutrophils (7%), and divided neutrophils (1%). Therefore on day 16 treatment with filgrastim, antibiotic, and antifungal drugs was stopped. At that time a bone marrow biopsy was performed and showed the presence of a granulocyte line with the features of rejuvenation and with preserved maturation; the erythrocyte line was poorly represented, and single megakaryocytes were observed. Melanoma cells were not revealed within the bone marrow. The patient was discharged from hospital with the recommendation to take 128 mg oral methylprednisolone daily. After another 5 days the patient was admitted to the outpatient clinic with a history of elevated body temperature and persistent cough during fever episodes. Laboratory results showed elevated WBC 24.1 g/l; ANC 17 g/l; basophils 0.05 g/l; eosinophils 0.0 g/l; Hgb 7.5 mmol/l; PLT 128 g/l; CRP 19.7 mg/l. The steroid dose was maintained. After 2 weeks the cough and fever had subsided but the elevated body temperature still persisted. The laboratory results began to stabilize but still were outside the normal reference range: WBC 12.3 g/l; ANC 10.6 g/l; Hgb 7.4 mmol/l; PLT 500 g/l; CRP 14.8 mg/l. The patient started to reduce the dose of steroids. After 5 weeks leukocytes, neutrophils, and platelets dropped to normal values but the patient developed deeper anaemia (Hgb 5.7 mmol/l). He was still on oral methylprednisolone 32 mg daily. In 12/2011 the patient developed symptomatic progression within the brain and died shortly thereafter.

Discussion

Treatment with ipilimumab is associated with irAEs occurring in 80% of all patients. Grade 3–5 irAEs are observed in 7–13% of patients treated with 3 mg/kg ipilimumab, while a higher dose (10 mg/kg) was shown to be associated with G3–4 irAE toxicity in 22–39% of patients [7–10]. The most frequently observed irAEs are dermatitis and gastrointestinal disorders (diarrhea, colitis). Less commonly noted irAEs include hepatitis, hypophysitis, hypothyroidism, neuropathy, and iritis/inflammation of the ciliary body [5]. Most of the irAE occur during the induction phase of ipilimumab treatment (consisting of 4 cycles; a maintenance phase dosing schedule is not approved and was tested only in clinical trials). These irAEs exhibit a characteristic pattern in the timing of their occurrence. The derma-
ological irAEs usually occur after 2–3 weeks, hepatitis and gastrointestinal disorders after 6–7 weeks, and endocrinopathies after approximately 9–10 weeks following the first ipilimumab infusion. The treatment guidelines recommend that low-grade irAEs should be managed symptomatically. Persistent or high-grade irAEs usually require treatment with corticosteroids (oral or intravenous), and in the case of refractory irAEs patients may require treatment with more potent immunosuppressive drugs such as infliximab for colitis or mycophenolate mofetil for hepatitis events [5].

There are several potential causes of neutropenia in cancer patients. This phenomenon may be associated with the cytotoxic effect of chemotherapy or radiotherapy, bone marrow metastases, systemic infections (bacterial, viral, fungal), some concomitant medications, or antineutrophil antibodies. In patients with neutropenia the risk of infection is higher and is related to the grade and duration of neutropenia. According to the European Society of Medical Oncology (ESMO) guidelines ‘febrile neutropenia (FN) is defined as an oral temperature > 38.5 °C or 2 consecutive readings of > 38.0 °C for 2 h and an ANC < 0.5 g/l (grade 4 neutropenia), or expected to fall below 0.5 g/l’. In 5% of patients with solid tumors and 11% with particular hematological malignancies febrile neutropenia results in death due to infectious complications [11].

In 2009, Akhtari et al. [6] published a case report of a patient treated with ipilimumab 10 mg/kg in a compassionate program, who developed febrile neutropenia with an ANC of 0.038 g/l (CTCAE G4). The patient’s differential revealed 4.8% granulocytes and 88.1% lymphocytes. The investigators noted that neutropenia was related to the presence of anti-neutrophil antibodies in the patient’s serum (anti-platelet auto-antibodies were also detected in that patient). Moreover the investigators ruled out other possible causes of neutropenia, suggesting that it was an ipilimumab-induced autoimmune adverse event. However the authors were unable to directly explain the cause of thrombocytopenia (CTCAE G4) occurring after a longer period of time from the onset of neutropenia, which was the primary reason for the patient’s hospitalization and administration of a multi-drug supportive treatment. There is evidence from animal models that ligation of CTLa-4 present on B-cells can inhibit B-cell effector function such as anti-body production. Moreover CTLA-4 is associated with decreased production of interferon-gamma by CD8+ T cells. Among others the above observations confirm that enhanced non-specific antibody represents one of several immune mechanisms activated by ipilimumab-based blockade of CTLa-4 [12, 13].

We report a case of a metastatic melanoma patient treated with low-dose ipilimumab, who suffered from febrile neutropenia with agranulocytosis in the blood smear. The leukocyte peripheral blood smear revealed primarily lymphocytes (75%), monocytes (25%), and single blasts. In our patient thrombocytopenia was not observed. The cause of this serious adverse event is unknown. Serum for the detection of anti-neutrophil antibodies was not collected from the patient, and bone marrow biopsy was performed after the neutropenia resolved. Also viral infection such as parvovirus B19, Epstein-Barr virus, cytomegalovirus, human immunodeficiency virus, and hepatitis A, B and C virus was not ruled out during the time of severe neutropenia persistence. However neutropenia due to administration of concomitant medications was excluded in this patient. Also metastases to the bone marrow were ruled out.

According to Akhtari et al. [6] it can be assumed that the neutropenia observed in our patient might also have been caused by anti-neutrophil antibodies associated with ipilimumab administration. Moreover the onset of grade 4 neutropenia in our patient, which occurred after 3 cycles of ipilimumab treatment, was similar to the timing of occurrence of other irAEs observed during anti-CTLA4 therapy. However the mechanisms of action of irAEs (associated with autoreactive lymphocyte activation) and antineutrophil antibody production are different. Due to lack of the necessary diagnostic tests the cause of febrile neutropenia in our patient remains unknown. However the possibility that such an adverse event may be associated with CTLA-4 inhibition must be taken into consideration in patients treated with ipilimumab.

Disclosure Statement

The authors declare no conflict of interest.

References


Iplimumab – Febrile Neutropenia


