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Sunitinib Induced Immune Thrombocytopenia

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Sunitinib is an orally administered multi-targeted tyrosine kinase inhibitor and has been approved for the treatment of advanced renal cell carcinoma (RCC). It is well known that sunitinib induces hematologic adverse events, such as neutropenia, anemia, and thrombocytopenia, primarily through myelosuppression. Here, we report that the first case of immune-thrombocytopenia occurred in a patient receiving sunitinib for the treatment of metastatic RCC. The thrombocytopenia was refractory to repeated platelet transfusion. The bone marrow aspiration study revealed an increased number of megakaryocytes. No thrombotic microangiopathy was seen. The thrombocytopenia was successfully treated with high-dose corticosteroid, although intravenous immunoglobulin administration was not effective. These findings suggest that an immune-mediated mechanism was responsible for the thrombocytopenia in this patient, which developed during sunitinib administration. (Kitakanto Med J 2011；61：175～177)

Key words：sunitinib, renal cell carcinoma, drug-induced thrombocytopenia

Introduction

Sunitinib is an orally administered multi-targeted tyrosine kinase inhibitor, which was approved by the FDA for the treatment of advanced renal cell carcinoma (RCC) in the United States. In Japan, it was also approved by the Ministry of Health, Labour and Welfare in June 2008. Hematologic adverse events such as neutropenia, thrombocytopenia, and leukopenia are common as Grade 3 or 4 abnormalities.[1]

We report a case of severe thrombocytopenia that was refractory to repeated platelet transfusion in a metastatic RCC patient treated with sunitinib. The thrombocytopenia was caused by an immune-mediated mechanism rather than myelosuppression.

Case report

A 64 year-old man received 50 mg sunitinib daily for the treatment of advanced clear cell carcinoma of the right kidney combined with brain metastasis. Before the sunitinib therapy, his white blood cell count (WBC) was 6×10^9/L, and his platelet (PLT) count was 242×10^9/L. At day 17 after the start of sunitinib therapy, his WBC and PLT had decreased to 2.5×10^9/L and 53×10^9/L, respectively. Although sunitinib was discontinued immediately, his thrombocytopenia progressed to 3.0×10^9/L, persisted for 9 days after the withdrawal of sunitinib, and was refractory to multiple transfusions of platelet concentrate (Fig. 1). The past medical history included diabetes and hypertension.

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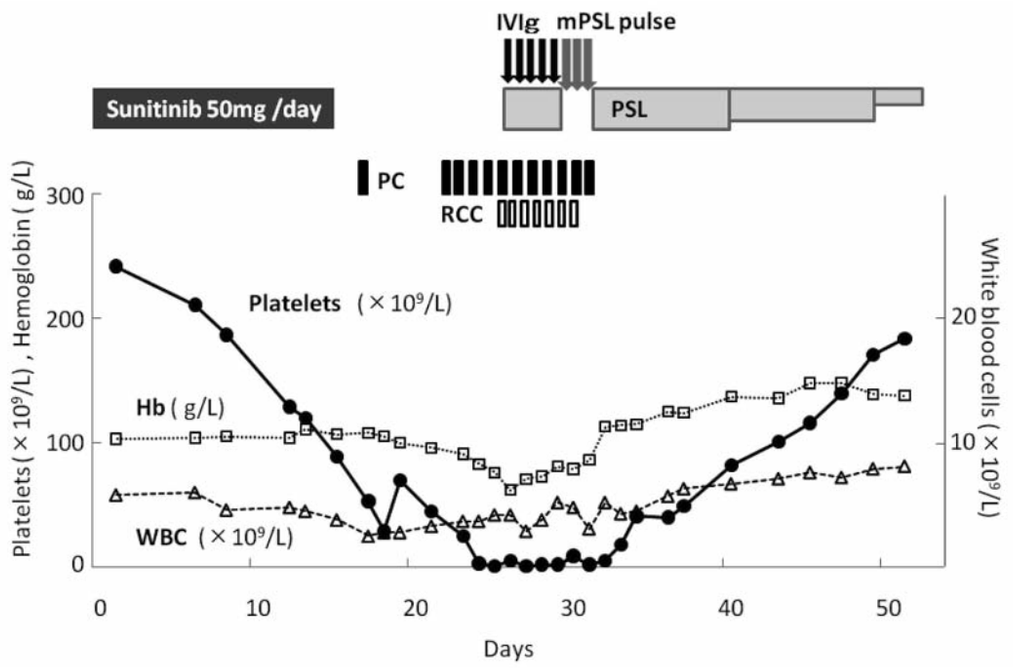

Fig. 1 Initial treatment with PSL and IVIG failed. After mPSL pulse therapy (1 g/day for 3 days) followed by PSL (1 mg/kg) the patient's platelet count increased. His platelet count did not drop after the PSL dose was tapered. Abbreviations: IVIG, intravenous immunoglobulin; mPSL, methylprednisolone; PSL, prednisolone; PC, platelet concentrate; RCC, red cell concentrate

He had not received any medication that inhibited CYP3A4. A physical examination revealed no fever, lymphadenopathy, or hepatosplenomegaly. Hemorrhaging of the oral cavity, epistaxis and petechiae of the extremities were observed, and he suffered from upper abdominal pain and massive melena. Gastrointestinal fiberscopy disclosed gastric cancer, which was thought to have caused his anemia. The patient received a red blood transfusion in addition to a platelet transfusion. His laboratory data was as follows: hemoglobin (Hb): 7.1 g/dl, WBC: 4.2×10^9/L and PLT: 5.0×10^9/L. Coagulation tests were normal. There were no data suggesting hemolytic anemia, and his liver and kidney function were normal. The patient's level of platelet-associated immunoglobulin G (PAIgG) was elevated (215ng/10^7 cell; normal range: 9-25ng/10^7 cell), but no anti-HLA antibody was detected. A peripheral blood smear showed neither dysplasia of myeloid cells nor platelet aggregation, and no schistocytes were detected. A bone marrow aspiration study showed a normal karyotype; 46, XY, and normal cellularity with an increased number of megakaryocytes, which led to a diagnosis of immune-mediated thrombocytopenia.

Based on the above diagnosis, we treated him with prednisolone (1 mg/kg/day) and intravenous immunoglobulin (IVIG: 400mg/kg/day) 5 days from day 10 after the cessation of sunitinib. Since his platelet count did not recovery and he had massive melena, he needed platelet and RBC transfusions day after day. Then methylprednisolone (mPSL) pulse therapy (1 g/day) was added for 3 days. On the day following the mPSL pulse therapy, his melena stopped and platelet transfusion was not needed. His platelet count improved to 101×10^9/L at 10 days after mPSL pulse therapy. After achieving remission, the prednisolone dose was tapered, and prednisolone therapy had been stopped.

Discussion

Sunitinib is approved for the treatment of advanced renal cell carcinoma as a first-line medication. In a phase 3 trial, grade 3 adverse events, which occurred in approximately 5% of patients, included anemia and thrombocytopenia. Grade 3 neutropenia was reported in approximately 15% of cases.[1] The hematological toxicity of sunitinib is believed to be caused by the suppression of hematopoietic stem cells in bone marrow via blocking VEGFR signaling.[2] In our case, pancytopenia appeared at 12 days after the beginning of sunitinib. Neutropenia recovered immediately after the discontinuation of sunitinib, and anemia was caused by bleeding from the gastric cancer. However, thrombocytopenia persisted even after the cessation of sunitinib and was refractory to multiple platelet transfusions. The number of megakaryocytes was increased in the bone marrow. These findings indicated that the severe thrombocytopenia was

immune-mediated rather than being due to myelosuppression. The thrombocytopenia aggravated melena, and he needed RBC transfusions day after day. Thrombotic microangiopathy is another cause of sunitinib-associated thrombocytopenia, as described by Kapiteijn et al.[3] However, thrombotic microangiopathy was ruled out in our case due to the absence of red blood cell fragmentation and laboratory data suggesting hemolysis.

Immune thrombocytopenia is mediated by antiplatelet autoantibodies, which accelerate platelet destruction and inhibit their production. Most cases involve primary (idiopathic) thrombocytopenia of unknown etiology, whereas others are attributed to coexisting conditions, such as connective tissue autoimmune diseases or infectious disease. Drugs also have the capability of inducing immune thrombocytopenia. Drug-induced immunoreaction of platelets arises through diverse mechanisms, based on antibody production in the presence of a sensitizing drug.[4,5] After the sensitized medication is discontinued, bleeding symptoms usually subside within 1 or 2 days and platelet counts return to normal in 4–8 days. For unknown reasons, thrombocytopenia occasionally persists for 1 or 2 weeks.[6] Trinkaus et al. also reported immune thrombocytopenia during the course of sunitinib therapy for metastatic breast cancer.[7] In the report, her platelet count rapidly improved 7 days after the IVIG treatment and returned to her normal baseline after 2 weeks like common pattern of recovery as described above. In our case, it took longer time to recover. Thrombocytopenia sustained for 16 days after cessation of sunitinib. It took more than 4 weeks to return to normal platelet count. This was the point that our case differed from other drug induced ITP.

There have been two reports of immune thrombocytopenia associated with renal cell carcinoma.[8,9] In these reports, they considered that the thrombocytopenia was not associated with RCC itself. Of course we cannot rule out the possibility that the immune thrombocytopenia was related to RCC. However, it is conceivable that the sunitinib treatment administered for RCC was associated with his thrombocytopenia because it developed after sunitinib therapy, and we had to end the sunitinib treatment.

We show that sunitinib causes severe immune thrombocytopenia that is refractory to platelet transfusion and IVIG. To our knowledge, we report the first case of sunitinib induced immune-related thrombocytopenia during treatment for RCC. Although thrombocytopenia is common adverse effect of sunitinib, we should take notice immune-mediated mechanism, if thrombocytopenia persists.

References

1. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007 ; 356 : 115-124.
2. Gerber HP, Malik AK, Solar GP, et al. VEGF regulates haematopoietic stem cell survival by an internal autocrine loop mechanism. Nature 2002 ; 417 : 954-958.
3. Kapiteijn E, Brand A, Kroep J, et al. Sunitinib induced hypertension, thrombotic microangiopathy and reversible posterior leukencephalopathy syndrome. Ann Oncol 2007 ; 18 : 1745-1747.
4. Cines DB, Bussel JB, Liebman HA, et al. The ITP syndrome : pathogenic and clinical diversity. Blood 2009 ; 113 : 6511-6521.
5. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. N Engl J Med 2007 ; 357 : 580-587.
6. Aster RH, Curtis BR, McFarland JG, et al. Drug-induced immune thrombocytopenia : pathogenesis, diagnosis, and management. J Thromb Haemost 2009 ; 7 : 911-918.
7. Trinkaus M, Trudeau M, Callum J. Drug-induced immune thrombocytopenic purpura secondary to sunitinib. Curr Oncol 2008 ; 15 : 152-154.
8. Yoshinaga A, Hayashi T, Ohno R, et al. A case of renal cell carcinoma associated with idiopathic thrombocytopenic purpura. Hinyokika Kiyo 2005 ; 51 : 3773-80.
9. Klimberg I, Drylie DM. Renal cell carcinoma and idiopathic thrombocytopenic purpura. Urology 1984 ; 23 : 293-296.