CASE REPORT

Continuous use of enzalutamide in a patient who developed enzalutamide-induced thrombocytopenia

Atsuko Sato, Takeo Kosaka, Mototsugu Oya

Department of Urology,
Keio University School of
Medicine, Tokyo, Japan

Correspondence to
Dr Takeo Kosaka,
takemduro@gmail.com

Accepted 5 November 2015

SUMMARY

Drug-induced thrombocytopenia (DIT) is known to be caused by many drugs. In daily clinical practice, it is not uncommon to observe cases of thrombocytopenia related to enzalutamide. We report the case of a 69-year-old patient with metastatic castration-resistant prostate cancer (CRPC) who was started on enzalutamide at a dose of 160 mg/day. Two weeks after starting enzalutamide, asymptomatic thrombocytopenia (platelet count 14 000/ μ L) occurred. Enzalutamide was withdrawn and the patient received platelet transfusions. The platelet count recovered immediately. Because the prostate-specific antigen (PSA) level had started to fall during treatment with enzalutamide, the patient was restarted on enzalutamide, but at a dose of 80 mg/day. He has continued to use enzalutamide without developing thrombocytopenia and the PSA level has kept falling. This case suggests that it is possible to again use enzalutamide in patients who have developed enzalutamide-induced thrombocytopenia.

hormone agonist and bicalutamide. The PSA level fell to a nadir of 0.05 ng/mL in May 2009. After 70 months on CAB, the PSA level started to rise. The patient stopped taking bicalutamide in October 2013, when his PSA level was 0.97 ng/mL. Although the PSA level continued to rise to 3.47 ng/mL, he was started on flutamide in December 2014. The PSA level did not decrease; thus, on 6 January 2015, he was prescribed enzalutamide at a dose of 160 mg/day when his PSA level was 3.59 ng/mL. Two weeks after starting enzalutamide, on 20 January 2015, asymptomatic thrombocytopenia was detected.

INVESTIGATIONS

The complete blood count was normal except for the platelet count, which was 14 000/ μ L. All other laboratory results were within normal limits. Hepatitis B antigen and hepatitis C antibody tests were negative.

BACKGROUND

Enzalutamide is a second-generation non-steroidal androgen receptor inhibitor that was found to extend the time until radiographic progression or death, improve overall survival and delay the initiation of chemotherapy, prolonging survival in patients with metastatic castration-resistant prostate cancer (CRPC) who had not received previous chemotherapy.¹ A few cases of thrombocytopenia considered to be induced by enzalutamide were reported in the postmarketing surveillance in Japan. But there is no consensus on how to use enzalutamide once drug-induced thrombocytopenia (DIT) has been resolved. We report a case of a patient who could take enzalutamide at a reduced dose, safely, after earlier having experienced DIT induced by enzalutamide.

CASE PRESENTATION

We submit a case of a 69-year-old man with a medical history of controlled hypertension, dislipidosis and hypothyroidism, who presented with an elevated prostate-specific antigen (PSA) level of 349.7 ng/mL (normal range 0–4 ng/mL), in November 2006. Prostate needle biopsy revealed an adenocarcinoma of Gleason score 7 (4+3). CT scan demonstrated metastatic lymph nodes. Bone scan was negative for metastatic lesions. The patient was diagnosed as having prostate cancer in clinical stage T4N1M0.

The patient was prescribed combined androgen blockade (CAB) with a gonadotrophin-releasing

DIFFERENTIAL DIAGNOSIS

In some cases, other malignant diseases or bone metastatic lesions of a malignant disease can cause thrombocytopenia. Autoimmune diseases, infections and other drugs, as well as some foods, can account for isolated thrombocytopenia. In addition to infection, some tumours can produce chronic disseminated intravascular coagulation (DIC). Although rarely, a recent transfusion can also cause thrombocytopenia. Idiopathic thrombocytopenic purpura is a diagnosis of exclusion. If multiple lineage abnormalities are observed, they may suggest the existence of haematological disease.

In this case, complete blood count and examination of peripheral blood smear only showed the platelet problem. The patient had not received a transfusion. No drugs apart from enzalutamide had been administered. The results of tests had not suggested infectious disease, and the patient's previous CT scan and bone scan did not demonstrate other malignant disease or bone metastatic lesions. We suspected that enzalutamide had induced thrombocytopenia because the platelet count had immediately fallen after he started taking it.

TREATMENT

The patient was admitted to our hospital and enzalutamide was withdrawn. Platelet transfusions were given for 2 days, during which the platelet count rose to 22 000/ μ L—it had begun recovering immediately after stopping enzalutamide. The platelet count was 60 000/ μ L on the sixth day of admission.

CrossMark

To cite: Sato A, Kosaka T, Oya M. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-212567

Figure 1 Prostate-specific antigen level and platelet count during treatment with enzalutamide. The arrows show the dates of platelet transfusion (Flu, flutamide; Enza, enzalutamide; GnRH, gonadotrophin-releasing hormone).

Figure 2 CT images showing intrapelvic lymph node. The arrows show the metastatic lymph node.

OUTCOME AND FOLLOW-UP

Although enzalutamide was considered to have caused severe thrombocytopenia, the PSA level started to fall since enzalutamide was initiated (figure 1). We proposed options such as restarting enzalutamide or substituting it with abiraterone or docetaxel, which, in Japan, are available for CRPC. The patient consented to restart use of enzalutamide and started to take it again on 17 February 2015. The daily dose was reduced to 80 mg/day. The PSA level was 2.69 ng/mL and the platelet count was 185 000/ μ L at that time. Up to the present, the patient has continued taking enzalutamide without showing any tendency to develop thrombocytopenia. His PSA level fell to 0.82 ng/mL in July 2015. In addition, the CT showed that the intrapelvic lymph node had decreased in size from 10 to 5 mm (figure 2).

DISCUSSION

DIT may be caused by many drugs through non-immune or immune mechanisms. Some drugs inhibit megakaryocytopoiesis and produce isolated thrombocytopenia. However, many drugs induce thrombocytopenia by accelerating platelet clearance through immune and less often through non-immune mechanisms.² In case of DIT, the suspected drug should be withdrawn immediately. Platelet transfusions and intravenous immunoglobulin may be required when thrombocytopenia is severe or if the patient presents bleeding symptoms.³ When DIT results from chemotherapy, reducing the dose intensity is a common measure if the regimen is effective or the alternative regimens are not considered to be sufficient for the treatment.⁴ A previous systematic review reported that DIT occurred <1 day to

3 years (median, 14 days) after the causative drug was initiated. The time to recovery of platelet count varied from 1 to 30 days (median, 7 days).⁵

In previous phase 3 trials, similar rates of adverse events with fatigue, diarrhoea, back pain and hot flashes were observed, more common with enzalutamide than with placebo.^{1 6} Hypertension was reported at a higher rate in the enzalutamide group in PREVAIL. But thrombocytopenia was not reported in these studies.

In the postmarketing surveillance carried out in Japan, it was found that, in the patients treated with enzalutamide, thrombocytopenia had occurred in a few cases. Consequently, when treating patients with enzalutamide, one must be vigilant regarding the risk of thrombocytopenia. However, there have been no reports of thrombocytopenia related to enzalutamide, so there has been no discussion as to whether enzalutamide can be

Learning points

- It might be possible for a patient who has drug-induced thrombocytopenia caused by enzalutamide to continue treatment with this drug, safely, at a reduced dose.
- Continuing treatment with enzalutamide should be considered when it has proved to be effective against the main medical condition.

continued or not when thrombocytopenia is observed, or if enzalutamide can be continued and at what dose. If DIT related to enzalutamide had occurred by immune mechanisms in our patient, the DIT would have occurred again after the re-challenge with the drug. This case, however, suggests that it is possible to use enzalutamide again once DIT has ameliorated.

Twitter Follow Takeo Kosaka at @takemduro

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Beer TM, Tombal B. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med* 2014;371:1755–6.
- 2 Aster RH, Curtis BR, McFarland JG, *et al.* Drug-induced immune thrombocytopenia: pathogenesis, diagnosis, and management. *J Thromb Haemost* 2009;7:911–18.
- 3 Arnold DM, Nazi I, Warkentin TE, *et al.* Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev* 2013;27:137–45.
- 4 Kuter DJ. Managing thrombocytopenia associated with cancer chemotherapy. *Oncology (Williston Park)* 2015;29:282–94.
- 5 George JN, Raskob GE, Shah SR, *et al.* Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med* 1998;129:886–90.
- 6 Scher HI, Fizazi K, Saad F, *et al.* Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367:1187–97.

Copyright 2015 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow