A case of dacarbazine, nimustine, vincristine, and interferon beta (DAVFeron) therapy for oral malignant melanoma induced unexpected acute severe thrombocytopenia

TAKAAKI KAMATANI, TOMOHIKO KUTSUNA, DAISUKE SATO, YASUTO YOSHIHAMA, SEIJI KONDO, TATSUO SHIROTA and SATORU SHINTANI

Abstract: Drug-induced thrombocytopenia is an uncommon but serious side effect. In some cases, it can prove fatal if not taken care of urgently. We report the case of a 70-year-old Japanese female with malignant melanoma at clinical stage of II, T2N0M0, according to the criteria for oral cancer treated with surgery followed by concomitant dacarbazine, nimustine, vincristine, and interferon beta (DAVFeron) therapy. When she was being evaluated for adjuvant DAVFeron therapy after 3 courses, she developed acute severe progressive thrombocytopenia requiring platelet transfusion. Thrombocytopenia was reversible in few days without further therapeutic intervention. Bone marrow involvement was excluded. The mechanism of this side effect remains unclear. The patient’s platelet count remained normal for more than 12 months thereafter. Clinicians must be aware of this rare, but serious side effect. Herein, we report a case of acute thrombocytopenia after DAVFeron therapy that occurred in an oral malignant melanoma patient.

Key words: Malignant melanoma, DAVFeron therapy, Thrombocytopenia

Introduction

The discovery of isolated thrombocytopenia in a patient who is taking chemotherapy presents a challenging clinical problem. Hematological toxicity is observed in nearly 40% of patients receiving dacarbazine (DTIC), nimustine (ACNU), vincristine (VCR), and interferon beta (IFN-β) (DAVFeron) therapy. Although an episode of delayed-onset neutropenia associated with DAVFeron therapy has been reported, acute thrombocytopenia is extremely rare side effect. Herein, we report a case of acute thrombocytopenia that occurred after DAVFeron therapy in an oral malignant melanoma patient.

Case report

A 70-year-old Japanese female patient with a diagnosis of malignant melanoma of the hard palate (Fig. 1) at clinical stage of II, T2N0M0 according to the criteria for oral cancer, received 3 courses of adjuvant DAVFeron therapy after surgery. Chemotherapy menu includes intravenous administration of ACNU 100mg (60mg/m²) and VCR 1mg (0.6mg/m²) on day 1, and DTIC 100mg (60mg/m²) from day 1 to day 5. In addition, INF-β (300×10^9U/day) was injected into the hard palate from day 1 to day 5 to amplify the treatment effect (Fig. 2).

There were no abnormal findings on routine blood test, hematocrit, or a urine test before treatment. Although leukocytopenia as an adverse event, the grade of severity was 3 according to Radiation Therapy Oncology Group (RTOG) toxicity criteria, was seen once in a second course, the prescribed treatment was completed well without any interruptions. Three weeks after 3 courses of DAVFeron therapy revealed low counts of platelet (1.7×10^9/L). According to RTOG toxicity criteria, toxicity was scored for grade 4 of thrombocytopenia. Leukocyte at
that time was $2500 \times 10^5/L$ and hemoglobin level was 9.7g/L. The patient was transfused with 10-units of platelets concentrates. Post-transfusion platelet count rebounded to $60 \times 10^9/L$ (Fig. 3). Thrombocytopenia was reversible in a few days without further therapeutic intervention. Her bone marrow aspiration and biopsy was subsequently performed. The bone marrow biopsy showed severely hypocellular or rather empty bone marrow and hardly any identifiable primitive progenitor stem cells, suggesting features of aplastic thrombocytopenia (drug-induced pancytopenia). She has not received any other therapy and her platelet count remained normal since then. There were no signs of a recurrence under evaluation by a computed tomography for more than 1 year thereafter (Fig. 4).

**Discussion**

A widely accepted treatment plan for malignant melanoma occurred in oral cavity has not been established. Little is known about the effect of adjuvant therapy in terms of clinical features in malignant melanoma occurred in oral cavity. DTIC is a chemotherapeutic agent widely used for the treatment of malignant melanoma in Western countries. Now, combination adjuvant therapy with DTIC, ACNU, and VCR (DAV) has been widely applied to the treatment of cutaneous malignant melanoma, and the therapeutic effects of this regimen are accepted$^4)$. In Japan, it is reported that the effectiveness rate with DAV combination therapy is approximately 30%. In superficial lesions, local injection of IFN-$\beta$ has been used in addition to DAV$^5)$. Advantage of a DAV + IFN-$\beta$ regimen in the effectiveness rate (65.1%) is better compared to

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**Table:**

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**Fig. 2** Regimen of DAVFeron therapy.

**Fig. 3** Platelet and white blood cell counts and hemoglobin during the operation and DAVFeron therapy period.

**Fig. 4** Intraoral view after treatment of surgery and chemotherapy.
that of DAV alone (46.2%) \(^6,7\). Although episodes of severe neutropenia have been reported after DAVFeron therapy about 16%, isolated acute thrombocytopenia is extremely rare only 2\%\(^1\). The mechanism of this side effect remains unclear. The important diagnostic issue is to differentiate between drug-induced thrombocytopenia and idiopathic thrombocytic purpura. The diagnosis of drug-induced thrombocytopenia can only be confirmed from the clinical symptoms and resolution of thrombocytopenia after discontinuing the suspected agent\(^8\). Among drug-induced thrombocytopenia, 9\% had major bleeding (0.8\% of patients died of bleeding), 28\% had minor bleeding, 39\% had trivial bleeding and 24\% had no bleeding symptoms despite a low platelet count\(^9\). The problem of drug-induced thrombocytopenia is clinically important. The patient presented here demonstrates a rare case of acute thrombocytopenia treated with DAVFeron therapy. While an absolute causal relationship of DAVFeron therapy with this potentially serious event cannot be established, clinicians need to be aware of this risk.

In conclusion, although the mechanism and incidence of DAVFeron therapy induced acute thrombocytopenia are still unclear, DAVFeron therapy should be used with caution in patients who have oral malignant melanoma of the hard palate, and clinicians must be aware of this rare, but serious, side effect.

This case was approved by the ethics committee of Showa University Dental Hospital.

References

2) http://www.rtog.org/members/toxicity/tox.html #blood/bone
口腔悪性黑色腫に対するDAVferon療法による急性の重篤な薬剤性血小板減少症の1例

鎌谷 宇明, 杉名 智彦, 佐藤 大典, 吉濱 泰斗, 近藤 誠二, 代田 達夫, 新谷 悟

薬剤性血小板減少症は稀な疾患であるが重篤な副作用であり, 時として適切な処置を施さなければ致命的である. 我々は70歳の日本人女性の口腔悪性黑色腫（T2N0M0, Stage II）に対し, ダカルバジン, 塩酸ニムスチン, 硫酸ビンクリスチン, インターフェロン β（DAVferon）療法を3クール施行したところ, 血小板輸血を必要とする急性の重篤な血小板減少症が生じた. 数日後には血小板は回復し, その後12ヶ月間再発はなかった. 骨髄抑制は否定されたがその原因は不明であった. 化学療法を行う上で, このような稀であるも重篤な副作用には注意しなければならない。

キーワード：悪性黑色腫, DAVferon療法, 血小板減少症