Case Reports in Oncology

Case Rep Oncol 2018;11:1–5

DOI: 10.1159/000485612
Published online: January 4, 2018

Case Report

Successful Treatment of Nivolumab-Resistant Multiple In-Transit Melanomas with Ipilimumab and Topical Imiquimod

Taku Fujimura Yumi Kambayashi Yota Sato Kayo Tanita
Sadanori Furudate Akira Tsukada Hisayuki Tono Akira Hashimoto
Setsuya Aiba

Department of Dermatology, Tohoku University Graduate School of Medicine, Sendai, Japan

Keywords
Nivolumab-resistant melanoma · Ipilimumab · Imiquimod

Abstract
Simultaneous or sequential, planned administration of ipilimumab could significantly enhance the antitumor effects of nivolumab in advanced melanoma patients. On the other hand, the efficacy of ipilimumab for nivolumab-resistant advanced melanoma is extremely poor. Therefore, additional supportive therapy for anti-PD-1 antibody therapy-resistant advanced melanoma has been widely investigated. In this report, we describe a case of multiple in-transit melanomas developing in a nivolumab-resistant patient successfully treated with ipilimumab in combination with imiquimod. Our present case suggested a possible therapy for nivolumab-resistant multiple in-transit melanomas using ipilimumab in combination with topical imiquimod.

KARGER

Taku Fujimura
Department of Dermatology
Tohoku University Graduate School of Medicine
Seiryo-machi 1-1, Aoba-ku, Sendai 980-8574 (Japan)
E-Mail tfujimura1@mac.com

Introduction

Simultaneous or sequential, planned administration of ipilimumab could significantly enhance the antitumor effects of nivolumab in advanced melanoma patients [1–3]. On the other hand, the efficacy of ipilimumab for nivolumab-resistant advanced melanoma is only 3.6% [4], suggesting the need for an additional supportive therapy for anti-PD-1 antibody therapy-resistant advanced melanoma. In this report, we describe a case of multiple in-transit melanomas developing in a nivolumab-resistant patient successfully treated with ipilimumab in combination with imiquimod. Our present case suggested a possible therapy for nivolumab-resistant multiple in-transit melanomas using ipilimumab in combination with topical imiquimod.

Case Report

A 67-year-old Japanese male visited our outpatient clinic with multiple nodules and prominent lymph edema on his left foot. He had been treated for acral lentiginous melanoma and had undergone excision of the tumors and left inguinal lymph node dissection (pT4aN3cM0 stage III C). In addition, after the surgical treatment, he had developed multiple pelvic lymph node metastases and was treated with nivolumab for 1 year with a complete response. The physical examination revealed multiple, skin-colored, dome-shaped, nodules on the left lower extremities. A biopsy specimen revealed dense infiltration of spindle-shaped atypical cells with pigmentation from the superficial dermis to the deep dermis (Fig. 1A). From the above findings, we diagnosed this patient as having multiple in-transit melanomas. We continued to administer nivolumab at 2 mg/kg every 3 weeks with intensity-modulated radiotherapy (5 Gy, 6 fractions). Four months after the radiation therapy, multiple in-transit metastases on the scrotum (Fig. 1B) and right external iliac lymph node had developed. Then, we administered ipilimumab (3 mg/kg every 3 weeks). In addition, we topically administered 5% imiquimod 3 weeks after the first administration of ipilimumab. Six weeks after we had started to administer topical imiquimod, all in-transit melanoma lesions had disappeared with scaring (Fig. 1C); however, the right external iliac lymph node remained swollen.

Discussion

Immune checkpoint inhibitors, such as nivolumab and ipilimumab, significantly prolong the overall survival and improve the response rate of unresectable metastatic melanoma [1–3]. Therefore, the enhancement of antitumor effects of anti-PD-1 antibody has been widely investigated [1–6]. Indeed, Larkin et al. [1] reported that the rate of overall survival at 3 years was 52% in the nivolumab group and 34% in the ipilimumab group. Moreover, simultaneous administration of nivolumab and ipilimumab or sequential, planned switching to the administration of nivolumab followed by ipilimumab significantly improved the response rate, suggesting that these methods are among the most effective protocols for unresectable metastatic melanoma, though the ratio of immune-related adverse events was also significantly increased [2, 3]. On the other hand, recently, Fujisawa et al. [4] reported that the response rate of nivolumab followed by ipilimumab was extremely low in nivolumab-resistant patients in spite of the development of severe immune-related adverse events. These reports

suggested the need for a combined therapy that enhances the antitumor effects of ipilimumab for nivolumab-resistant advanced melanoma patients.

Imiquimod is an immunomodulatory, small-molecule compound in the imidazoquinoline family that induces antitumor effects through Toll-like receptor 7 [7, 8]. Recent reports suggested that topical imiquimod is useful for the treatment of melanoma both in mice and humans [7–10]. Furudate et al. [7] reported the immunomodulatory effects of imiquimod on tumor-associated macrophages, leading to a decrease in the ratio of regulatory T cells and an increase in the cytotoxic T cells in vivo. In another report, Singh et al. [10] reported that intratumoral administration of Toll-like receptor 7/8 agonist significantly enhanced the therapeutic effect of anti-CTLA4 antibody to suppress B16F10 melanoma growth in vivo. Moreover, Joseph et al. [11] described two cases of in-transit melanoma patients successfully treated with ipilimumab together with topical imiquimod. From the above findings, we hypothesized that topical imiquimod could enhance the antitumor effects of ipilimumab even in nivolumab-tolerated melanoma patients. Indeed, the administration of ipilimumab in combination with ipilimumab dramatically reduced the multiple in-transit melanomas in our present case. As in a mouse model, imiquimod might decrease regulatory T cells to abrogate the immunosuppressive microenvironment at the tumor site [7]. Since this report presents only a single case, further cases are needed to clarify the efficacy of ipilimumab in combination with imiquimod.

Statement of Ethics

The authors have no ethical conflicts to declare.

Disclosure Statement

The authors have no conflicting interests to declare.

Author Contributions

Taku Fujimura: conception and design, acquisition of clinical data, analysis and interpretation of data, writing, review, and/or revision of the manuscript, and study supervision. Yumi Kambayashi: acquisition of clinical data. Yota Sato: acquisition of clinical data. Kayo Tanita: acquisition of clinical data. Sadanori Furudate: acquisition of clinical data. Akira Tsukada: acquisition of clinical data. Hisayuki Tono: acquisition of clinical data. Akira Hashimoto: acquisition of clinical data. Setsuya Aiba: study supervision.

References

▶1 Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, Lao CD, Wagstaff J, Schadendorf D, Ferrucci PF, Smylie M, Dummer R, Hill A, Hogg D, Haanen J, Carlino MS, Bechter O, Maio M, Marquez-Rodas I, Guidoboni M, McArthur G, Lebbé C, Ascierto PA, Long GV, Cebon J, Sosman J, Postow MA, Callahan MK, Walker D, Rollin L, Bhore R, Hodi FS, Larkin J: Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–1356.

▶2 Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur

GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD: Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.

▶3 Weber JS, Gibney G, Sullivan RJ, Sosman JA, Slingluff CL Jr, Lawrence DP, Logan TF, Schuchter LM, Nair S, Fecher L, Buchbinder EI, Berghorn E, Ruisi M, Kong G, Jiang J, Horak C, Hodi FS: Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): an open-label, randomised, phase 2 trial. Lancet Oncol 2016;17:943–955.

4 Fujisawa Y, Yoshino K, Otsuka A, Funakoshi T, Fujimura T, Yamamoto Y, Hata H, Tanaka R, Yamaguchi K, Nonomura Y, Hirai I, Furudate S, Okuhira H, Imafuku K, Aoki M, Matsushita S: Retrospective study of advanced melanoma patients treated with ipilimumab after nivolumab: analysis of 60 Japanese patients. J Dermatol Sci 2017, Epub ahead of print.

▶5 Fujimura T, Hidaka T, Kambayashi Y, Furudate S, Kakizaki A, Tono H, Tsukada A, Haga T, Hashimoto A, Morimoto R, Yamaguchi T, Takano T, Aiba S: Phase I study of nivolumab combined with IFN-β for patients with advanced melanoma. Oncotarget 2017;8:71181–71187.

▶6 Fujimura T, Kambayashi Y, Furudate S, Hidaka T, Sato Y, Tanita K, Tono H, Tsukada A, Hashimoto A, Aiba S: Successful treatment of multiple in-transit melanomas on the leg with intensity-modulated radiotherapy and immune checkpoints inhibitors: reports of two cases. J Dermatol 2017;44:592–595.

▶7 Furudate S, Fujimura T, Kambayashi Y, Kakizaki A, Hidaka T, Aiba S: Immunomodulatory effect of imiquimod through CCL22 produced by tumor-associated macrophages in B16F10 melanomas. Anticancer Res 2017;37:3461–3471.

▶8 Drobits B, Holcmann M, Amberg N, Swiecki M, Grundtner R, Hammer M, Colonna M, Sibilia M: Imiquimod clears tumors in mice independent of adaptive immunity by converting pDCs into tumor-killing effector cells. J Clin Invest 2012;122:575–585.

▶9 Higgins HW 2nd, Lee KC, Galan A, Leffell DJ: Melanoma in situ: part II. Histopathology, treatment, and clinical management. J Am Acad Dermatol 2015;73:193–203; quiz 203–204.

▶10 Singh M, Khong H, Dai Z, Huang XF, Wargo JA, Cooper ZA, Vasilakos JP, Hwu P, Overwijk WW: Effective innate and adaptive antimelanoma immunity through localized TLR7/8 activation. J Immunol 2014;193:4722–4731.

▶11 Joseph RW, Cappel M, Tzou K, Bagaria S, Gilstrap C, Swaika A, Jambusaria-Pahlajani A: Treatment of in-transit and metastatic melanoma in two patients treated with ipilimumab and topical imiquimod. Melanoma Res 2016;26:409–412.

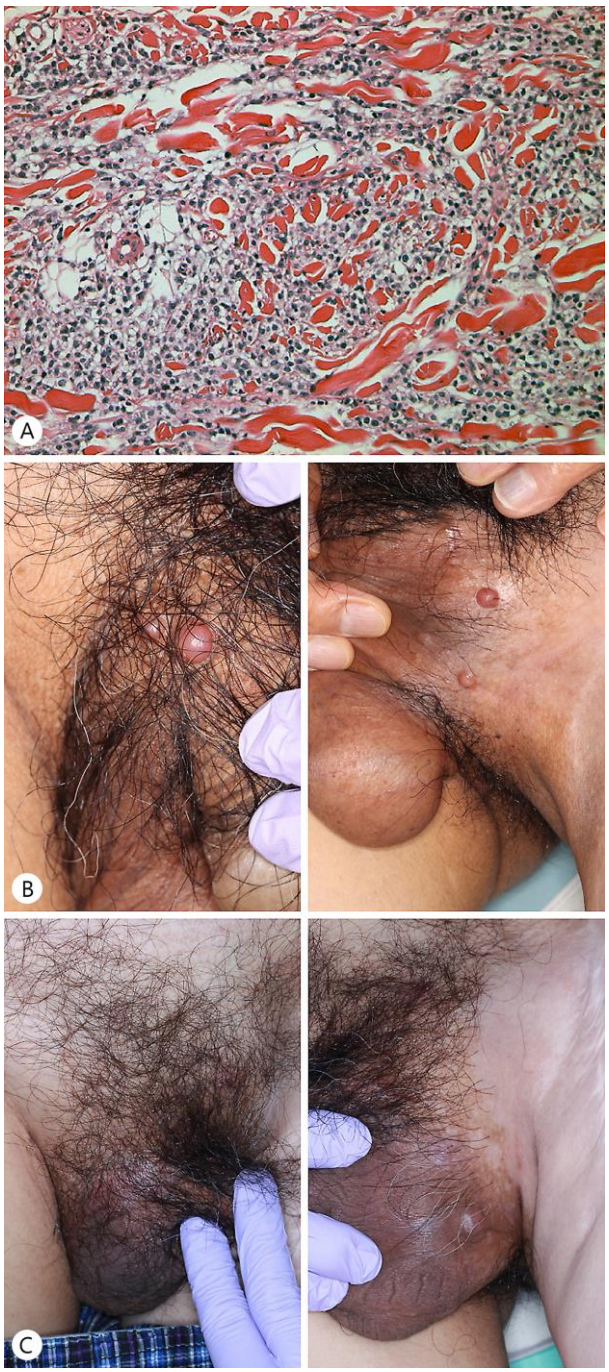

Fig. 1. Dense infiltration of spindle-shaped atypical cells with pigmentation from the superficial dermis to the deep dermis (**A**). Multiple in-transit metastases on the scrotum that are ingrown: before imiquimod treatment (**B**) and after imiquimod treatment (**C**).