A case of malignant melanoma that developed multiple metastases after switching from interferon-beta to pegylated interferon-alpha-2b as adjuvant therapy

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A case of malignant melanoma that developed multiple metastases after switching to pegylated interferon-alpha-2b from interferon-beta for adjuvant therapy

Short title: Adjuvant therapy with type 1-IFN

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Dear Editor

Although therapeutic strategies for melanoma have advanced, melanoma remains incurable owing to frequent recurrence and metastasis, requiring effective adjuvant therapy [1]. Adjuvant therapy with interferon (IFN)-α-2b improves recurrence-free and overall survival [1]. Pegylated (PEG)-IFN-α-2b, an IFN molecule covalently bound to polyethylene glycol, can maintain longer-sustained effects with less frequent injection than unpegylated-IFN-α-2b, and has been utilized as a global standard adjuvant therapy for high-risk melanoma [1-3]. However, Japan has adopted adjuvant therapy with IFN-β (either daily therapy or maintenance therapy every 2-4 weeks) or DAV Feron (dacarbazine, nimustine, vincristine, and IFN-β) [1,3,4], and there is no consensus as to whether patients already receiving these therapies can be safely switched to PEG-IFN-α-2b. Here, we report a patient with melanoma who rapidly developed multiple metastases after switching to PEG-IFN-α-2b from IFN-β.

A 49-year-old Japanese man presented with a black nodule on his left leg (Fig. 1A). It was excised with 20-mm margins, and histopathological examination revealed aggregation of atypical melanocytic cells that were melan-A positive in both the epidermis and dermis (Fig. 1B, C). Satellite lesions and regional lymph node metastases were also observed. He was diagnosed with stage IIIc (T3bN3M0, nodular type, *BRAF*^{V600E}-mutated) melanoma with a 3.21-mm Breslow Depth Index and a Clark IV Level, and selected IFN-β maintenance adjuvant therapy (3 million IU monthly). Although he had been stable for 1 year with IFN-β adjuvant therapy, he switched to PEG-IFN-α-2b adjuvant therapy after its approval in Japan (6 μg/kg weekly during an 8-week induction phase, followed by a weekly maintenance phase of 3 μg/kg). One month after switching, he developed fatigue, and, after 2 more months, he suddenly developed anemia

(decrease in hemoglobin from 14 g/dL to 6.4 g/dL). Other biochemical data, including lactate dehydrogenase and liver enzymes, were within the normal range with both adjuvant therapies. Endoscopy and computed tomography detected the development of new duodenum and liver metastases (Fig. 1D-F). Dabrafenib (150 mg twice daily) plus trametinib (2 mg once daily) was administered. Two months after temporary improvement, brain metastasis developed (Fig. 1G). Despite nivolumab (3 mg/kg every 2 weeks) and whole brain radiotherapy (45 Gy) administration, he died within 4 months.

PEG-IFN-α-2b has a significant effect as adjuvant therapy for high-risk melanoma [1-3]. No major safety concerns were determined in Japanese patients compared to non-Japanese patients, and PEG-IFN-α-2b was approved in Japan in 2015 [1,3]. Meanwhile, as IFN-β and DAV Feron adjuvant therapy for melanoma have been covered by Japanese National Health Insurance since 1985, many patients have undergone adjuvant therapy with IFN-β or DAV Feron [1,3,4]. Recently, some reports have revealed that DAV Feron adjuvant therapy showed no significant improvement in the survival of stage II and III melanoma patients [1,5]. Many patients are concerned with switching adjuvant therapy, and there is no evidence as to whether patients already receiving IFN-β or DAV Feron can be safely switched to PEG-IFN-α-2b. To our knowledge, we provide the first case of melanoma that rapidly developed metastases after switching adjuvant therapy to PEG-IFN-α-2b from IFN-β. The possibility that the switch affected the development of metastases cannot be denied.

IFN-α and IFN-β are type-1 IFNs that can exert an antitumor effect on melanoma [6-9]. Although they are considered to exert a similar effect by activating the same signaling pathway [8,9], they have also been reported to have potentially different cellular and clinical effects on

melanoma [6,7,10]. IFN-β1a shows a greater anti-proliferative and pro-apoptotic effect, and IFN-α2b shows greater inhibitory effects on lymph node metastasis [6]. Additionally, IFN-β more potently induces genes that regulate anti-proliferative and apoptosis-inducing effects [7]. PEG-IFN-α-2b was recently approved and has garnered much attention. Meanwhile, several reports have revealed significant efficacy of IFN-β adjuvant therapy on melanoma in experimental systems and in a retrospective clinical analysis [3,4,10]. IFN-β adjuvant therapy remains an option in the treatment of melanoma [3,4,10].

Based on our findings, clinicians should be aware that some melanoma patients might rapidly develop metastasis after switching to PEG-IFN-α-2 from IFN-β for adjuvant therapy. Better understanding of the specific mechanisms of IFN-α and IFN-β is necessary to predict which patients will benefit from which adjuvant therapy and the best method for patients already receiving IFN-β or DAV Feron adjuvant therapy to be safely switched to PEG-IFN-α-2b.

Sincerely,

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Figure Legend

Figure 1. Clinical appearance and histopathological examination

A) A black nodule was identified on the lower left leg.

B) A dense proliferation of atypical melanocytic cells with melanin pigment in the epidermis and dermis (hematoxylin and eosin stain; original magnification: 200×).

C) Aggregation of atypical cells in the epidermis and dermis were positive for melan-A (200×).

D) No nodular shadow was detected on computed tomography 1 month before switching adjuvant therapy to pegylated (PEG)-IFN-α-2b from interferon (IFN)-β.

E) A nodular shadow in the duodenum was detected on computed tomography 3 months after switching adjuvant therapy to PEG-IFN-α-2b from IFN-β.

F) A nodular shadow in the liver was detected on computed tomography 3 months after switching adjuvant therapy to PEG-IFN-α-2b from IFN-β.

G) A well-enhanced nodule in the brain was detected by magnetic resonance imaging 8 months after switching adjuvant therapy to PEG-IFN-α-2b from IFN-β.

European Journal of Dermatology, Fukumoto et al., Figure 1