CASE REPORT

Successful treatment with gefitinib after Stevens–Johnson syndrome associated with afatinib therapy in a patient with adenocarcinoma of the lung

Tomoyuki Otsuka¹ · Aya Tanaka² · Hiroaki Azukizawa^{2,3} · Shoko Sasaki¹ · Mikako Ishijima¹ · Takanori Matsuki¹ · Akio Osa¹ · Takeshi Nakatani¹ · Muneyoshi Kuroyama¹ · Haruhiko Hirata¹ · Takashi Kijima¹

Received: 30 July 2016 / Accepted: 30 October 2016 / Published online: 5 November 2016
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Abstract We report a case of a 65-year-old woman with stage IV lung adenocarcinoma who experienced Stevens–Johnson syndrome (SJS) during afatinib therapy. The patient received afatinib as the first-line therapy after the confirmation of harboring an exon 19 deletion mutation in the epidermal growth factor receptor (EGFR) gene. The patient presented with multiple erythematous papules mainly on the body trunk and thigh 32 days after afatinib administration. Subsequently, diffuse erosions of oral mucosa and purpuric macules with flat atypical targets emerged. Skin biopsy specimen showed the histology compatible with epidermal necrosis and the patient was diagnosed as having SJS. The symptoms of SJS were recovered by systemic steroid and immunoglobulin treatment. Gefitinib was administered as the third-line therapy after the second-line therapy with carboplatin plus pemetrexed had failed. Tumor shrinkage was obtained shortly and has been maintained without the recurrence of SJS. Rechallenge of tyrosine kinase inhibitor by gefitinib could be an alternative treatment option in patients who experienced SJS by afatinib.

Keywords EGFR-TKI · Afatinib · Gefitinib · Non-small-cell lung cancer · Stevens–Johnson syndrome

Introduction

Afatinib is an irreversible inhibitor of the erythroblastosis oncogene B (ERBB) family that is able to inhibit the tyrosine phosphorylation of kinase domain of the epidermal growth factor receptor (EGFR), human EGFR receptor 2 (HER2), HER4, and the transphosphorylation of ERBB3 [1]. Afatinib is superior to the standard chemotherapy in patients with non-small-cell lung cancer (NSCLC) harboring EGFR mutations. Phase III studies have shown that afatinib is well tolerated. Common adverse events were diarrhea, rash or acne, paronychia, and mucositis [2, 3]. We report a patient with adenocarcinoma of the lung who experienced life-threatening Stevens–Johnson syndrome (SJS) as an adverse event during afatinib therapy, and were able to be safely treated by switching to gefitinib.

Case report

A 65-year-old Japanese female never smoker was referred to our institution due to an abnormal shadow in the left lung on a chest X-ray film. A computed tomography (CT) scan of the chest revealed a tumor in the left upper lobe. The histopathological examination of a tissue obtained by bronchoscopic biopsy revealed that the tumor was adenocarcinoma. The whole body examination confirmed that the disease was stage IV with bone and brain metastases (cT2aN2M1b). Mutation analysis with the PNA-LNA clamp method [4] of the diagnostic specimen revealed the existence of a deletion in exon 19 of the EGFR gene.

✉ Takashi Kijima
tkijima@imed3.med.osaka-u.ac.jp

¹ Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

² Department of Dermatology, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita, Osaka 565-0871, Japan

³ Department of Dermatology, Nara Medical University, 840 Shijo-Cho, Kashihara, Nara 634-8521, Japan

Fig. 1 Physical findings on day 40 after afatinib treatment. Oral mucosal lesions (a). Diffuse erythema papules on body trunk (b), and thigh (c)

After having received a whole-brain radiation therapy (WBRT), oral afatinib therapy was initiated with a once-daily dose of 40 mg. Because of an adverse event of anorexia, the dose was reduced to 30 mg on day 12. The patient presented with multiple erythematous papules mainly on the body trunk and thigh on day 32. Afatinib treatment was discontinued on day 34, though the tumor shrinkage had been obtained. Six days later, the patient exhibited multiple purpuric coalescing macules and vesicles on face, body trunk, and thigh (Fig. 1). Diffuse erosion of oral mucosa and purpuric macules with flat atypical targets were observed. She had a body temperature of 38.0 °C, general fatigue, and complained of conjunctivitis. Nikolsky's sign was positive. Routine laboratory examinations revealed abnormal alanine aminotransferase (ALT, 86 IU/L, NL: 0 ~ 40 IU/L). Bacterial cultures from blood, urine, and sputum revealed no evidence of bacterial infection. Skin biopsy specimen showed diffuse epidermal necrosis, subepidermal blister formation between the epidermis and dermis, and infiltration of lymphocytes (Fig. 2). According to these results, she was diagnosed as having SJS.

The patient was treated with 400 mg/kg/day of human immunoglobulins for 5 consecutive days and 1000 mg/day of methylprednisolone for 3 days as steroid pulse therapy, and thereafter followed by 50 mg/day of prednisolone [5]. The patient recovered from SJS after 2 weeks of intensive therapy (Fig. 3). Prednisolone was tapered off and finally discontinued over 2 months.

Two months later, drug patch tests were performed to determine the culprit drug. Patch tests were performed at 1

Fig. 2 Histopathological findings of biopsy on the patient's abdomen showed diffuse epidermal necrosis, subepidermal blister formation between the epidermis and dermis, and infiltration of lymphocytes (Hematoxylin and eosin stain; original magnification, $\times 200$)

and 10% in petrolatum with afatinib, minocycline, sulfamethoxazole/trimethoprim, and lansoprazole. Only afatinib at 10% showed grade 1 positive reaction at 72 h suggesting that afatinib was the most likely responsible drug.

The patient once met the criteria of partial response by afatinib therapy, but the tumor regrew after discontinuation of the therapy. Thereafter, the patient received carboplatin plus pemetrexed as the second-line therapy with achieving the criteria of stable disease, which failed after four cycles. Six months after, afatinib treatment was discontinued; gefitinib therapy was commenced at an oral dose of

Fig. 3 Clinical course of lesions on the back, on the date of diagnosis (a) and on day 14 after the initiation of therapy (b). Erosions were resolved on day 14

250 mg daily as the third-line therapy. A CT scan examination revealed the shrinkage of the tumors after 2 months which met the criteria of partial response. The patient is still treated with gefitinib for 8 months without acquired resistance, and SJS has not recurred.

Discussion

SJS is a rare, acute, and life-threatening muco-cutaneous disease characterized by extensive necrosis and detachment of the epidermis [6]. The most frequent causes of SJS are drugs, including antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs, and allopurinol. Infection with microorganisms, such as herpes simplex virus and mycoplasma, is also known as a possible cause of SJS. None of infectious disease was diagnosed in our case. Afatinib is considered to be the most likely cause of muco-cutaneous reactions based on the results of drug patch tests in this case.

While there is no definitive treatment guidance for SJS, systemic corticosteroids, cyclosporine, plasma exchange, and immunoglobulin have been used in practice. Aihara et al. [5] reported the efficacy of systemic immunoglobulin in combination with corticosteroids in SJS in a prospective study.

The incidence of the cutaneous adverse events which are common in the treatment with EGFR tyrosine kinase inhibitors (TKIs) is more frequent with afatinib than the first-generation EGFR-TKIs, gefitinib, or erlotinib [7]. In two-phase III studies, LUX-Lung 3 [2], and LUX-Lung 6 [3], grade 3 rash or acne occurred in 14.6–16.2% of patients in afatinib arm. However, the exact mechanism of the development of rash associated with the treatment of EGFR-TKIs is not completely understood. To our knowledge, there has been only one report of SJS associated with afatinib treatment [8]. SJS and Toxic epidermal necrolysis (TEN) are difficult to rescue due to its rapid progression

unless it cannot be diagnosed at an early stage. In order not to misdiagnose incipient SJS, physicians should pay attention not only for cutaneous complications but also for mucosal involvement during afatinib treatment.

Mockenhaupt et al. [9] reported that SJS usually occurs within 8 weeks after the initiation of the responsible medication. Indeed, in our case, SJS occurs on day 32. Up to 8 weeks after the initiation of afatinib, close observation should be recommended. Huang et al. reported a case of TEN related to pemetrexed plus cisplatin and gefitinib combination therapy [10]. We worried about if SJS would recur after administration of gefitinib in our case. Therefore, the patient was carefully examined with respect to mucosal involvement during gefitinib treatment. The present case has been successfully treated with gefitinib without recurrence of SJS. As one of the explanations, we speculate that afatinib and gefitinib have structurally different antigenicity to cause a delayed-type hypersensitivity reaction.

EGFR-TKI is the key drug that brings about clinical benefit to patients with NSCLC harboring EGFR mutations. Takeda et al. [11] reported that patients who had to discontinue the first EGFR-TKI treatment due to adverse events can still benefit substantially from switching to another EGFR-TKI, because the profile and the frequency of several adverse events are different among three EGFR-TKIs. Several reports have stated that patients with NSCLC who had developed severe interstitial lung disease related to gefitinib treatment could be safely switched to erlotinib [12, 13]. Our results suggest that even when SJS occurred during afatinib therapy, gefitinib therapy is promising as effective alternative treatment strategy.

Compliance with ethical standards

Conflict of interest Takashi Kijima received lecture fee from AstraZeneca Co. Ltd. and Boehringer Ingelheim Co. Ltd., and the others declare that they have no conflict of interest.

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