Case Report

The Use of *Ziziphus spina-christi* Extract in Treating Erlotinib (Tarceva®) Associated Rash: A Case Report

Ali M. Alzahrani^a Asma A. Alzahrani^b Abdullah A. Alsharm^a

^aOncology Department, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia;

^bPharmaceutical Care Department, National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia

Keywords

Ziziphus spina-christi · Epidermal growth factor receptor · Rash · Non-small cell lung cancer

Abstract

The most common side effect for cancer patients using epidermal growth factor receptor inhibitors (EGFRI) is the development of an itchy papulopustular rash. In severe cases, the patients are forced to stop taking the medications, hence affecting treatment outcomes. We herein report a case of a 50-year-old patient who developed a papulopustular rash after starting erlotinib. He treated himself with *Ziziphus spina-christi* leaves which is a plant well known for its anti-inflammatory and antibacterial properties in the middle east. We hypothesize that the anti-inflammatory, soothing, and antibacterial activity of the *Ziziphus* tree might actually represent a possible better treatment of the rash than available treatments, particularly in patients on EGFR blockers, and hence improve treatment outcomes.

© 2019 The Author(s)
Published by S. Karger AG, Basel

Introduction

Many epidermal growth factor receptor inhibitors (EGFRI) are associated with skin toxicity which might be very cumbersome and in severe cases might force patients to stop taking the medications [1]. Erlotinib (Tarceva®) is a tyrosine kinase inhibitor and it blocks the epidermal growth factor receptor (EGFR) [2].

The EGFR is a transmembrane glycoprotein 170-kd. The EGFRs are found in the epithelial tissues and hair follicles and they are responsible for the processes of proliferation and keratocytokine diversification. EGFR's increased expression can be found in some cancers, including up to 80% of non-small cell lung cancers (NSCLC) and colonic carcinomas; it is usually linked to their increased malignancy. EGFR has become an attractive target for cancer therapy development since EGFR inhibition may weaken the tumor growth. Nowadays, there are two groups of EGFR blockers: the tyrosine kinase inhibitors (gefitinib, erlotinib) and IgG1 monoclonal antibodies against the EGFR (cetuximab, panitumumab). Patients with locally advanced NSCLC or NSCLC with metastases were treated with application of at least one chemotherapy schedule, but this method was not successful. Currently, erlotinib (Tarceva®) is the recommended treatment in these cases [2].

In the plant kingdom, *Ziziphus* is a genus of about 40 species of shrubs and trees. The best-known species is *Z. ziziphus* (Jujube). Other species include *Z. spina-christi* from southwestern Asia, *Z. lotus* from the Mediterranean region, *Z. mauritiana* (Ber) which is found from western Africa to India, and *Z. joazeiro* which grows in the Caatinga of Brazil. *Ziziphus* leaves are alternate, entire, with three prominent basal veins, and 2–7 cm (0.79–2.8 in) long, some species are deciduous, others evergreen [3]. Some species like *Z. mauritiana* Lam. and *Z. spina-christi* (L.) wild occur on nearly every continent and they have very nutritious fruits and are usually eaten fresh [3].

In Arab countries, *Z. spina-christi* is known as “SEDR” [4]. The trees are used traditionally in many skin and hair treatments [5]. Mainly to alleviate skin infections and improve the length and strength of hair [5–7]. The *Z. spina-christi* extract has an anti-inflammatory activity that shows significant inhibition of inflammation [8]. It demonstrates excellent activity against COX1 and COX2 with higher than 85% inhibition of prostaglandins [9]. *Z. spina-christi* contains compounds with cytotoxic activity when tested on different cancer cell lines [10] and the methanolic *Ziziphus* stem bark extract has a natural antibacterial potential [11].

We are reporting a case of lung cancer who was treated with erlotinib and developed a skin rash. The patient treated himself with minced leaves of *Z. spina-christi* and his rash disappeared completely.

Case Report

The patient, a 50-year-old male nonsmoker, presented in July 2015 with a history of cough, weight loss, and hemoptysis. The personal history revealed no comorbid conditions, no previous medical or surgical history of significance, and the patient did not drink alcohol. He worked as an accountant in one of the governmental companies in Riyadh. He lived all of his life in the central part of Saudi Arabia, mainly in Riyadh.

The CT scan of the chest showed a lung lesion 6 × 5 cm occupying the right middle lobe with several bone metastases all over the thoracic vertebrae. CT scan of the abdomen did not show other visceral metastases but there were few metastases in the lumbar vertebrae. Bone scan confirmed the widespread bone metastases mainly in the vertebrae. The CT-guided

biopsy revealed adenocarcinoma of the lung. He was started on cisplatin 75 mg/m² intravenous infusion over 1 h on day 1 and pemetrexed 500 mg/m² intravenous infusion over 10 min on day 1 to be repeated every 21 days. The tissue was sent abroad for EGFR and anaplastic lymphoma kinase testing. He had received 2 cycles of chemotherapy when he was found to be EGFR mutation positive and was subsequently shifted to Erlotinib 150 mg daily.

After 10 days of commencement of the treatment with erlotinib he started to develop a severe rash all over the body. It was an erythematous maculopapular rash associated with generalized itching. He was prescribed emollient creams.

However, he presented the next day with complete disappearance of the rash. He claimed not to have used any creams we had prescribed but *Z. spina-christi* grinded moistened leaves all over his body. On further follow-up, he had continued this practice for a few months with similar response until the rash disappeared completely.

Discussion

The treatment of NSCLC with EGFR blockers is considered first line in EGFR-mutant variants, with improvement in survival and quality of life [12]. The main side effect of such treatment is a skin rash which sometimes is very troublesome [1].

There are many hypotheses trying to explain the mechanism of rash development. The strongest possibility is that the release of inflammatory cytokines, especially NK1, causes apoptosis and skin damage [13]. The rash severity is divided into 4 degrees and ranges from mild erythematous rash to severe desquamation of the skin [2]. There are many reports indicating that the presence of a rash might be a good sign for possible response to the medication in the future [13].

Many guidelines have been published for treatment and prevention of rash with some success, but in general the improvement has been moderate. Treatment for the rash is mainly emollient creams, some antibiotics, and steroids [13].

The *Ziziphus* plant has been known for many years, its fruit is eaten as food and its barks, leaves, and roots are used as medicine. There are different types of this tree spread all over the world, but *Z. spina-christi* grows in the middle east [4]. Many people use its oil to strengthen the hair [7].

There are several studies on its constituents and its therapeutic effect on cell cultures and on animals. The main constituents of *Ziziphus* leaves are betulinic and ceanothic acids, various flavonoids, saponins, tannins, triterpenes, and cardiac glycosides. The *Z. spina-christi* extract has cyclopeptides, lipids, protein, and mucilage [4].

Several published papers have shown its antibacterial property and even suggested to extract new antibiotics from the tree [6]. Another trial found an anti-inflammatory material resembling steroids in leaf extract [8]. One study showed its antineoplastic behavior, while another one showed an antinociceptive behavior of the bark extract [4, 10]. In one study a cream made from the plant was used for the treatment of skin infections and ulcers, with good success [5].

Taking into consideration all these possible anti-inflammatory, soothing, and antibacterial activity of *Ziziphus* tree represents a possible good treatment of the rash developed after using the EGFR blockers and might prove beneficial for the patient. A phase I trial of using the *Ziziphus* cream in all patients on EGFR blockers is undergoing in order to discover a potential prevention and cure of the troublesome skin rash.

Statement of Ethics

The patient gave his verbal consent to publish this case report.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There are no funding sources for this case report.

Author Contributions

Ali Alzahrani attended and monitored the case, Asma Alzahrani interpreted the pharmacological effect of *Ziziphus spina* and the side effects of erlotinib, Abdullah Alsharm did the final revision of the case report to be published.

References

- 1 Kiyohara Y, Yamazaki N, Kishi A. Erlotinib-related skin toxicities: treatment strategies in patients with metastatic non-small cell lung cancer. *J Am Acad Dermatol*. 2013 Sep;69(3):463–72.
- 2 Owczarczyk-Saczonek A, Witmanowski H, Placek W. Acneiform rash during lung cancer therapy with erlotinib (Tarceva®). *Postepy Dermatol Alergol*. 2013 Jun;30(3):195–8.
- 3 Abalaka ME, Mann A, Adeyemo SO. Studies on in-vitro antioxidant and free radical scavenging potential and phytochemical screening of leaves of *Ziziphus mauritiana* L. and *Ziziphus spinachristi* L. compared with Ascorbic acid. *J Med Genet Genomics*. 2011 Feb;3(2):28–34.
- 4 Asgarpanah J, Haghighat E. Phytochemistry and pharmacologic properties of *Ziziphus spina christi* (L.) Willd. *Afr J Pharm Pharmacol*. 2012 Aug;6(31):2332–9.
- 5 Ali HS, Shehab NA, El-ahaj BM. Formulation and evaluation of herbal cream from *ziziphus spina* leaves extract. *Int Res J Pharm*. 2013 Jun;4(6):44–8.
- 6 Al-Bayatti K, Aziz F, Abdalah M. A Study of Antibacterial Activity of Cedar (*Zizyphus spinachristi* L.) on Bacterial Pathogens isolated from Skin Infections. *AJPS*. 2011;9(1):13–20.
- 7 Awadh Ali NA, Al Sokari SS, Gushash A, Anwar S, Al-Karani K, Al-Khulaidi A. Ethnopharmacological Survey of Medicinal Plants in Albaha Region, Saudi Arabia. *Pharmacognosy Res*. 2017 Oct-Dec;9(4):401–7.
- 8 Ismaiel S, Mahmoud E, Mahmoud A. Anti-Inflammatory Activity of Some Indigenous Sudanese Plants. *RJPP*. 2014 Jan-Mar;6(1):30–2.
- 9 Rodríguez Villanueva J, Rodríguez Villanueva L. Experimental and Clinical Pharmacology of *Ziziphus jujuba* Mills. *Phytother Res*. 2017 Mar;31(3):347–65.
- 10 Jafarian A, Zolfaghari B, Shirani K. Cytotoxicity of different extracts of arial parts of *Ziziphus spina-christi* on Hela and MDA-MB-468 tumor cells. *Adv Biomed Res*. 2014 Jan;3(1):38.
- 11 Sameera N, Mandakini B. Investigations into the antibacterial activity of *Ziziphus mauritiana* Lam. and *Ziziphus xylopyra* (Retz.) Willd. *IFRJ*. 2015 Jan;22(2):849–53.
- 12 Yamazaki N, Kiyohara Y, Kudoh S, Seki A, Fukuoka M. Optimal strength and timing of steroids in the management of erlotinib-related skin toxicities in a post-marketing surveillance study (POLARSTAR) of 9909 non-small-cell lung cancer patients. *Int J Clin Oncol*. 2016 Apr;21(2):248–53.