

# Plasma rich in growth factors for the treatment of rapidly progressing refractory corneal melting due to erlotinib in nonsmall cell lung cancer

Adriano Guarnieri, MD<sup>a,\*</sup>, Belén Alfonso-Bartolozzi, MD<sup>a</sup>, Gianfranco Ciuffo, MD<sup>a</sup>, Javier Moreno-Montañés, MD, PhD<sup>a</sup>, Ignacio Gil-Bazo, MD, PhD<sup>b</sup>

## Abstract

**Rationale:** Erlotinib, an antineoplastic agent, is indicated for the treatment of patients with advanced nonsmall cell lung cancer. Most common adverse events are manageable, although more severe ones require dose reduction or discontinuation of erlotinib treatment.

**Patient concerns:** We present a case of severe corneal ulcer treated with autologous plasma rich in growth factors.

**Diagnoses:** A 76-year-old woman with stage IVB (cT2a N0 M1c) lung cancer under erlotinib treatment presented with rapidly progressing corneal ulcer. Evolution was torpid and refractory to conventional treatment.

**Interventions:** Surgical options were dismissed because of the poor performance status of the patient. Despite temporary discontinuation of erlotinib treatment, the corneal ulcer continued to worsen with peripheral corneal neovascularization, stromal thinning, corneal edema, and profuse inflammation of the ocular surface.

**Outcomes:** Treatment with autologous plasma rich in growth factors prevented an imminent corneal perforation and improved the corneal ulcer for over a year of follow-up.

**Lessons:** Considering the poor results of conventional treatment, both medical and surgical, management of the inflammation of the ocular surface together with the stimulation of the healing processes through regenerative therapy such as PRGF, can be an option worth considering in these cases.

**Abbreviations:** EGF = Epidermal Growth Factor, EGFR = Epidermal Growth Factor receptor, FGF = Fibroblast Growth Factor, HGF = Hepatocyte Growth Factor, KGF = Keratinocytes Growth Factor, PDGF = Platelet-derived Growth Factor, PRGF = Plasma Rich in Growth Factors, TGF = Transforming Growth Factor, TK = tyrosine kinase.

**Keywords:** corneal ulcer, descemetocele, drug toxicity, EGFR-tyrosine kinase inhibitors, plasma-rich

## 1. Introduction

Erlotinib (Tarceva; Genetech Roche, Basel, Switzerland) is an antineoplastic agent indicated for the treatment of patients with metastatic nonsmall cell lung whose tumors show epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations. EGFR is a transmembrane tyrosine kinase (TK) receptor that is frequently expressed in many epithelial tumors, and the aberrant signal through this receptor is

associated with cellular neoplastic proliferation, resistance to apoptosis and angiogenesis, thus playing an important role in controlling cellular growth and differentiation.<sup>[1]</sup> Erlotinib is first-generation quinazoline derivative that selectively and reversibly inhibits the TK activity of EGFR. As a small molecule, it exerts its action intracellularly,<sup>[2]</sup> while monoclonal antibodies against EGFR act at the membrane extracellular binding site.<sup>[1]</sup>

It is known that EGFR is expressed on the surface of cells in tissues throughout the body, including the skin, hair follicles, and ocular surface epithelia.<sup>[3,4]</sup> Although EGFR TK inhibitors show a generally predictable and manageable toxicity, being acneiform rash and diarrhea, the most common adverse events, several ocular side effects have been published,<sup>[5-8]</sup> from some case reports describing mild discomfort to others showing severe corneal ulcers refractory to medical or surgical treatments.<sup>[9]</sup> Anti-EGFR treatment discontinuation,<sup>[10]</sup> or its dose reduction,<sup>[11]</sup> is considered to be the only option in these cases. Here, we report a case of severe corneal melting successfully treated with plasma rich in growth factors (PRGF-Endoret; BTI Biotechnology Institute, Vitoria-Gasteiz, Spain) without definitive erlotinib discontinuation.

## 2. Case report

Written informed consent was obtained and approved by the Institutional Review Board for Human Studies and Ethics Committee of Clínica Universidad de Navarra, University of Navarre.

Editor: Vishal Jhanji.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

The authors report no conflicts of interest.

<sup>a</sup> Department of Ophthalmology, <sup>b</sup> Department of Oncology, Clínica Universidad de Navarra, Navarre, Spain.

\* Correspondence: Adriano Guarnieri, Department of Ophthalmology, Clínica Universidad de Navarra, Avda. Pío XII, 36, Pamplona, Navarre 31008, Spain (e-mail: aguarneri@unav.es).

Copyright © 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2017) 96:22(e7000)

Received: 23 March 2017 / Received in final form: 25 April 2017 / Accepted: 26 April 2017

<http://dx.doi.org/10.1097/MD.0000000000007000>

A 76-year-old, Caucasian, retired woman, diagnosed with cT2a N0 M1c (stage IVB) lung cancer harboring an EGFR 19 exon deletion, was referred to our practice due to progressive vision loss in her left eye. She had previously received whole brain radiotherapy for multiple brain secondary lesions and at the time of visit, she was in her second month under first-line erlotinib 150 mg once a day (QD), having experienced partial response to the treatment. Her best corrected visual acuity was 20/200 in the left eye and the slit-lamp examination showed interstitial keratitis and subepithelial fibrosis (Fig. 1A). Her right eye was normal with 20/20 vision. The rest of the examination was normal in both eyes and nonpreservative lubricant, HyloComod eye-drops (Brill Pharma, Barcelona, Spain) and Thealoz Duo gel (Laboratoires Thea, Clermont, France), with low-dose corticoid topical therapy was initiated.

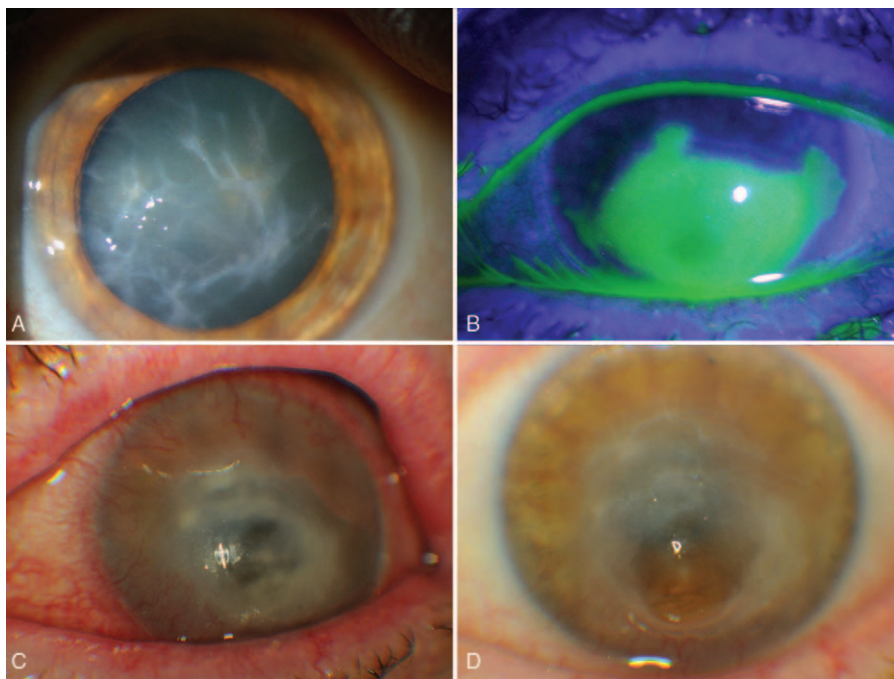
The evolution in the left eye resulted torpid and a persistent corneal defect appeared 11 months later (Fig. 1B). Topical antibiotics, such as moxifloxacin (Vigamox, Alcon, Switzerland) and tobramycin (Tobrex, Alcon, Switzerland), were added 4 times daily, and Cacicol (Laboratoires Thea, Clermont, France), a heparan sulfate analog that promotes epithelialization,<sup>[12]</sup> was added 1 eye-drop every 48 hours for a total of 6 doses. The corneal defect continued to deteriorate showing severe stromal thinning, so topical corticoid was discontinued and PRGF-Endoret eye-drops were added, 4 times daily. Temporary discontinuation of erlotinib treatment was indicated, while surgical options were dismissed because of the poor performance status of the patient. Despite this, the corneal ulcer continued to worsen with peripheral corneal neovascularization 360°, important stromal thinning, corneal edema, and profuse inflammation of the ocular surface (Fig. 1C). Assessing the risk to benefit ratio for the patient per her performance status, after 2 weeks of treatment discontinuation, it was decided to reintroduce erlotinib (at a lower dose of 100 mg QD) and reinstate therapy with topical

corticoids to control the inflammation of the ocular surface, maintaining the rest of the eye treatment with topical antibiotics and PRGF. Fifteen days later, a significant improvement was observed (Fig. 1D). A contact lens was tried but afterwards removed due to intolerance caused by the ectasia with descemetocoele that prevented a good adaptation. In subsequent visits, corticoids were tapered and eventually suspended, while corneal integrity was maintained using conservative medical treatment with the same lubricants and PRGF for over a year of follow-up (Fig. 2).

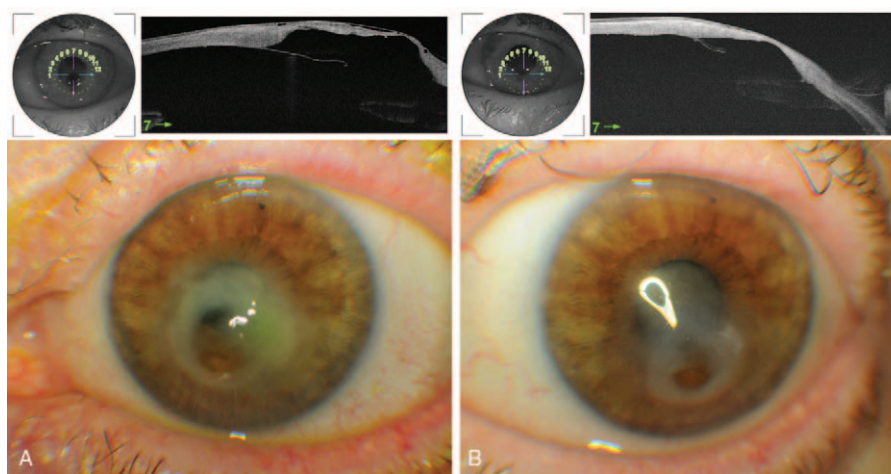
### 3. Conclusion

The binding of the epidermal growth factor (EGF) activates its receptor through phosphorylation, stimulating the proliferation of corneal epithelial cells.<sup>[13]</sup> This signaling pathway is considered paramount to the healing of corneal epithelial defects and animal tests have shown that the administration of systemic EGFR inhibitors delay corneal healing.<sup>[13]</sup> There are reported cases of ocular perforations that have required keratoplasty,<sup>[9]</sup> corneal melting treated with autologous serum,<sup>[10]</sup> and epithelial defects that have persisted despite topical treatment<sup>[8]</sup> in patients treated with standard doses of erlotinib. Treatment with autologous PRGF can theoretically decrease the effect of high molecular weight EGFR inhibitors, as they compete for extracellular EGFR binding sites. However, low molecular weight inhibitors act intracellularly, inhibit the intracellular phosphorylation of EGFR, and would not affect the inhibition of enzymatic activity, so erlotinib treatment should be suspended in order to see some improvement or even to achieve spontaneous healing.<sup>[11]</sup>

In our case, no relevant changes were observed when treatment with erlotinib was temporarily discontinued for 2 weeks, despite that this drug has a half-life of about 36 hours.<sup>[2]</sup> Even when erlotinib treatment was resumed, our patient showed anatomical



**Figure 1.** Slit-lamp examination of the left eye through follow-up. (A) Interstitial keratitis with marked subepithelial fibrosis, without epithelial defect and no inflammatory reaction in the anterior chamber. (B) Large epithelial defect compromising visual axis. (C) Increased stromal thinning, corneal edema, corneal neovascularization 360° and persistent epithelial defect. (D) Descemetocoele with surrounding haze with less corneal neovascularization and smaller epithelial defect.



**Figure 2.** Vertical scan of corneal OCT of the left eye showing evolution through 4 months' follow-up. (A) Extreme corneal thinning (descemetocoele) with a high risk of perforation with unstructured corneal stroma. (B) Less haze around descemetocoele with thicker and better organized corneal stroma. No inflammatory reaction and visual axis is clearer than before.

and symptomatic improvement under treatment with topical PRGF. After 1 year of follow-up, corneal integrity was maintained avoiding perforation and an increased corneal thickness in the periphery of the descemetocoele was observed (Fig. 2), as well as less epithelial damage. To the best of our knowledge, this is the first reported case in which PRGF have significantly contributed to corneal healing in a patient under erlotinib treatment.

Some of the growth factors present in PRGF, such as EGF, hepatocyte growth factor (HGF), and keratinocytes growth factor (KGF), have been described as key regulators in corneal wound healing, employing different signaling pathways in charge of stimulating the proliferation of epithelial cells. In the corneal stroma, PRGF is able to mediate these processes thanks to other factors such as transforming growth factor (TGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF).<sup>[14]</sup> The different signaling pathways through which the different growth factors operate, other than EGFR, may explain the clinical improvement in our patient despite continuing treatment with erlotinib. Corneal injury triggers the infiltration of immune cells into the cornea from the limbal vessels, necessary for proper wound healing, but too many immune cells accumulation also results in delayed wound closure, demonstrating the delicate balance of inflammatory events needed during corneal healing.<sup>[15]</sup> In this case presented, the corneal damage improvement with the treatment provided allowed the patient to further maintain erlotinib treatment continuing to systemically benefit from the drug for more than a year after the adverse event was diagnosed.

Considering the poor results of conventional treatment, both medical and surgical, we believe that management of the inflammation of the ocular surface together with the stimulation of the healing processes through regenerative therapy, such as PRGF, can be an option worth considering in these cases of poor prognosis.

## References

- [1] Castillo L, Etienne-Grimaldi MC, Fischel JL, et al. Pharmacological background of EGFR targeting. *Ann Oncol* 2004;15:1007–12.
- [2] Bareschino MA, Schettino C, Troiani T, et al. Erlotinib in cancer treatment. *Ann Oncol* 2007;18(Suppl 6): vi35–41.
- [3] Yano S, Kondo K, Yamaguchi M, et al. Distribution and function of EGFR in human tissue and the effect of EGFR tyrosine kinase inhibition. *Anticancer Res* 2003;23(5A):3639–50.
- [4] Liu Z, Carvajal M, Carraway CA, et al. Expression of the receptor tyrosine kinases, epidermal growth factor receptor, ErbB2, and ErbB3, in human ocular surface epithelia. *Cornea* 2001;20:81–5.
- [5] Methvin AB, Gausas RE. Newly recognized ocular side effects of erlotinib. *Ophthalm Plast Reconstr Surg* 2007;23:63–5.
- [6] Basti S. Ocular toxicities of epidermal growth factor receptor inhibitors and their management. *Cancer Nursing* 2007;30(Suppl 1):S10–6.
- [7] Zhang G, Basti S, Jampol LM. Acquired trichomegaly and symptomatic external ocular changes in patients receiving epidermal growth factor receptor inhibitors: case reports and a review of literature. *Cornea* 2007;26:858–60.
- [8] Johnson KS, Levin F, Chu DS. Persistent corneal epithelial defect associated with erlotinib treatment. *Cornea* 2009;28:706–7.
- [9] Saint-Jean A, Sainz de la Maza M, Morral M, et al. Ocular adverse events of systemic inhibitors of the epidermal growth factor receptor: report of 5 cases. *Ophthalmology* 2012;119:1798–802.
- [10] Chow VWS, Jhanji V, Chi SCC. Erlotinib-related corneal melting. *Ophthalmology* 2013;120: 1104.e1.
- [11] Morishige N, Hatabe N, Morita Y, et al. Spontaneous healing of corneal perforation after temporary discontinuation of erlotinib treatment. *Case Rep Ophthalmol Karger Publishers* 2014;5:6–10.
- [12] Arvola RPJ, Robciuc A, Holopainen JM. Matrix regeneration therapy: a case series of corneal neurotrophic ulcers. *Cornea* 2016;35:451–5.
- [13] Nakamura Y, Sotozono C, Kinoshita S. The epidermal growth factor receptor (EGFR): role in corneal wound healing and homeostasis. *Exp Eye Res* 2001;72:511–7.
- [14] Anitua E, Sanchez M, Merayo-Llodes J, et al. Plasma rich in growth factors (PRGF-Endoret) stimulates proliferation and migration of primary keratocytes and conjunctival fibroblasts and inhibits and reverts TGF-beta1-induced myodifferentiation. *Invest Ophthalmol Vis Sci* 2011;52:6066–73.
- [15] Reins RY, Hanlon SD, Magadi S, McDermott AM. Effects of topically applied vitamin D during corneal wound healing. *PLoS One* 2016;11: e0152889.