

Erlotinib and hair texture abnormal

Introduction

Erlotinib (Tarceva®) is an EGFR-tyrosinase inhibitor prescribed as first-line therapy in *non-small-cell lung carcinoma (NSCLC)* and *EGFR-activated mutations*. It is also indicated as switch into maintenance treatment for patients with *local advanced or metastasized NSCLC with EGFR activated mutations* and with *stable disease after first-line chemotherapy*. Furthermore, erlotinib is prescribed in patients with *metastasized pancreatic cancer* in combination with gemcitabine. Erlotinib was first registered on 19 September 2005 in Europe, as Tarceva® [1].

Epidermal growth factor receptors (EGFR) are present on the cell membrane of healthy cells and cancer cells. EGFR mutations can lead to activation of anti-apoptotic and proliferative signal transduction routes. Erlotinib is an epidermal growth factor receptor type I (EGFR/HER1) tyrosinekinase inhibitor, which inhibits intracellular phosphorylation of EGFR [1]. Erlotinib could therefore inhibit EGFR-mediated signal transduction in EGFR mutation-positive tumors, inhibiting proliferation of these tumor cells and induce cell death.

Hair texture changes have earlier been associated with drug treatments. Lareb previously published an article on hair texture changes from straight to curly hair after valproic acid treatment [2] and treatment with retinoids [3].

Reports

Until March 23rd 2022, Lareb received one report on changes in hair texture after erlotinib treatment.

NL-LRB-234988: This spontaneous report concerns a female aged 50-60 years old, with myalgia, arthralgia, edema hands, pain in hand, depressed mood, straight hair which curled and dermatitis following administration of erlotinib for non-small cell lung cancer. This report was marked as serious because the pain in hands disabled her from doing her job. Her hair changed from straight to thick small curls in 12 months after treatment start. During radiotherapy treatment she had stopped erlotinib use for one month. Beside radiation, she was not treated with other medication than erlotinib for non-small cell lung cancer.

Other sources of information

SmPC

The official product information of erlotinib mentions some hair-related changes, including: *alopecia*, *folliculitis* (common), *eyebrow changes* and *hirsutism* (excessive hair growth in a male-like pattern) (uncommon). *Eyelash changes* with following footnote: Including in-growing eyelashes, excessive growth and thickening of the eyelashes. The emergence of *curly hair* however is not mentioned [1].

Literature

In 1995 by Murillas *et al.* already showed in a mouse study that there is a relationship between EGFR and control of hair cycle progression [4]. Transgenic mice with dominant EGFR negative mutant in the hair follicle displayed short and waved pelage hair and curly whiskers, later resulting in alopecia.

Trichomegaly, persistent hair growth and other adverse hair reactions have also been described in literature [5-7]. And, two case reports and a case series on hair changes associated with EGFR inhibitors have been published [8-10].

Other databases

Additional reports were included from the Eudravigilance database. This database contained 57 reports on erlotinib and abnormal hair texture. When selecting only reports that mentioned 'curl' in the case narrative, 23 reports remained, which are described in the table below. The first eleven reports were spontaneous reports. Reports 12 until 23 were reported from clinical trials in the US.

Table 1. Reports on erlotinib and hair texture changes from the Eudragilance database.

	Case Report Number, Sender, report type, country, age, sex, primary source	Suspect, indication	Concomitant, and past drug therapy	Reaction List PT	Latency, Action taken, Outcome	Comments
1	AU-ROCHE-600165, Roche, spontaneous, Australia, 38, Female, Healthcare professional (Physician)	Erlotinib, Non-small cell lung cancer metastatic	Not reported She received cytotoxic chemotherapy prior to erlotinib use	Alopecia, Hair colour changes, Hair texture abnormal, Rash pustular	10 months	The author states that although abnormal scalp hair growth, including alopecia and curling have previously been described, patient's change of hair colour appears to be a new finding.
2	US-ROCHE-1236184 Roche, spontaneous, USA, female, Healthcare professional (Physician)	Erlotinib hydrochloride (Tarceva), unknown indication	Not reported	Diarrhoea, Dry skin, Hair texture abnormal, Muscle spasms, Rash	Recovering/ Resolving	Had change in hair as her hair became curly
3	US-ROCHE-1270507 Roche, spontaneous, USA, female, Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), unknown indication	Not reported	Diarrhoea, Hair texture abnormal, Purpura	Therapy ongoing, Recovering/ Resolving	She experienced change in hair curly.
4	US-ROCHE-1148542 Roche, spontaneous, USA, 71, female, Healthcare professional (Other health professional)	Erlotinib hydrochloride (Tarceva), Non-small cell lung cancer	Clonazepam, Nortriptyline, Nortriptyline hydrochloride	Bone lesion, Drug dependence, Epistaxis, Erythema, Hair texture abnormal, Lacrimation increased, Nail discolouration, Nail disorder, Nail growth abnormal, Nasopharyngitis, Onychomadesis, Rash erythematous, Rash pruritic, Rash pustular, Skin lesion, Therapeutic product effect decreased, Thermohyperaesthesia, Wound, Wound complication, Wound secretion		Her hair completely changed from long straight to curly and short
5	US-ROCHE-1565978 Roche, spontaneous, USA, 77, female, Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), Lung neoplasm malignant	Not reported	Alopecia, Diarrhoea, Hair texture abnormal, Nail discolouration, Nausea, Rash, Skin disorder		Curly eyelashes and hair loss
6	US-ROCHE-1660059 Roche, spontaneous, USA, 65, female, Healthcare	Erlotinib hydrochloride (Tarceva), Non-small cell lung cancer	Acetylsalicylic acid, Calcium carbonate, Polymyxin, Potassium gluconate	Acne, Blepharitis, Diarrhoea, Eye disorder, Hair growth abnormal, Hair texture abnormal,		Erratic hair growth, had changed hair texture and caused hair to be very curly. She skipped dose due

	professional (Physician)	Biopsy demonstrated an adenocarcinoma with findings consistent with stage IIIB disease gilbert syndrome	In 2005: She was treated with combined chemotherapy and radiation therapy, but relapsed 16 months later with bilateral pulmonary nodules. She started erlotinib in January 2015	Hordeolum, Hypokalaemia, Nausea, Rash, Rubber sensitivity, Skin disorder		to diarrhea. It was reported that she continued to have curly hair
7	US-ROCHE-1445262 Roche, spontaneous, USA, 68, female, Healthcare professional (Other health professional)	Erlotinib hydrochloride (Tarceva), Lung neoplasm malignant	Azithromycin, Colecalciferol, Clindamycin, Clindamycin hydrochloride, Clindamycin phosphate, Doxycycline, Hyclate, Erythromycin, Loperamide hydrochloride, Ketoconazole, Krill oil, Paracetamol	Diarrhoea, Drug ineffective, Dry eye, Dry skin, Hair texture abnormal Malignant neoplasm progression, Nasopharyngitis, Onychoclasia, Product dose omission issue, Rash, Skin reaction, Vision blurred	Not recovered/ Not resolved	Caused her naturally straight hair became curly and still it was curly. After therapy with erlotinib hydrochloride was stopped, her curly hair was persisting.
8	BR-ROCHE-1857582 Roche, spontaneous, Brazil, 80, Male, Healthcare professional (Physician)	Erlotinib hydrochloride (Tarceva), Non-small cell lung cancer	Ipratropium, Ipratropium bromide, Ipratropium bromide anhydrous, Ipratropium bromide monohydrate, Carboplatin, Apixaban, Pemetrexed, Pemetrexed disodium hemipentahydrate, Acetylsalicylic acid	Dermatitis acneiform, Hair texture abnormal, Infection, Lymphadenopathy, Onycholysis, Paronychia, Plaural effusion, Pleural thickening, Pneumonia, Pneumonitis, Skin exfoliation, Xerosis		Curly hair There was identification of a mutation of EGFR (detected exon 19 deletion).
9	US-ROCHE-1700077 Roche, spontaneous, USA, 72, Male, Non Healthcare professional (Other health professional)	Erlotinib hydrochloride (Tarceva), Started at 100 mg once daily Lung neoplasm malignant	Acetylsalicylic acid, difluprednate, Fluticasone propionate, Cefalexin, cefalexin monohydrate, Levofloxacin, Megestrol acetate, Pseudoephedrine hydrochloride, Guaifenesin, Polymyxin B sulfate, Trimethoprim, Polymyxin B, Montelukast, Montelukast sodium, Triamcinolone He had received radiation prior to the use of erlotinib.	Bronchitis, Decreased appetite, Dehydration, Drug ineffective, Dysgeusia, Gout, Hair texture abnormal, Hepatitis A, Herpes zoster, Muscle spasms, Nail discolouration, Nail infection, Neoplasm progression, Onychomadesis, Pneumonia, Pruritus, Rash, Sinusitis, Skin disorder		His hair was now curly
10	HK-ROCHE-2249805 Roche, spontaneous, Hong Kong, 75, Female, Healthcare professional (Other health professional)	Erlotinib, Lung adenocarcinoma stage IV with EGFR exon 21 Leu858Arg mutation	Benzylpenicillin, Prednisolone	Dry eye, Eyelid rash, Growth of eyelashes, Hair texture abnormal, Iridocyclitis, Nail dystrophy, Ulcerative keratitis		Curly and elongated eye lashes

11	NZ-ROCHE-2353846 Roche, spontaneous, New Zealand, Female, Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), Non-small cell lung cancer	Osimertinib, Osimertinib mesylate	Alopecia, Back pain, Decreased appetite, Dry skin, EGFR gene mutation, Hair disorder, Hair texture abnormal, Loss of personal independence in daily activities, Pulmonary oedema, Rash, Respiratory disorder		Curly and thinning hair
12	US-ROCHE-1155470 Report from studies United States of America 50 Female Healthcare professional (Physician)	Erlotinib hydrochloride (Tarceva), Bronchial carcinoma (EGFR) mutation with in the 19 deletion (T2N2M1)	Zolpidem, Zolpidem tartrate Clindamycin, Clindamycin phosphate, Estradiol potassium, Granisetron hydrochloride prochlorperazine Maleate, Prochlorperazine maleate, Hydrocodone bitartrate, Paracetamol Medical history included Stage IV non-small cell lung cancer of the right lung, metastases to spine (T12) with radiation therapy (RT)	Abdominal pain upper, Arthralgia, Back pain, Constipation, Dermatitis acneiform, Diarrhoea, Dry eye, Dry skin, Hair texture abnormal, Intestinal pseudo-obstruction, Large intestine perforation Madarosis, Mucosal inflammation, Onychoclasia, Stomatitis, Thirst	Dose reduced, Not Recovered/ Not Resolved	Curlier hair on head
13	US-ROCHE-1418197 Report from studies United States of America 70 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), unknown indication	Not reported	Gastrointestinal pain, Growth of eyelashes, Hair texture abnormal, Nausea Solar lentigo		Hair started to curl (straight hair curl)
14	US-ROCHE-1420914 Report from studies United States of America 52 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), Lung neoplasm malignant	Not reported	Alopecia Decreased appetite, Dermatitis acneiform, Diarrhoea , Growth of eyelashes, Hair growth abnormal, Hair texture abnormal, Hepatic enzyme increased, Liver function test increased, Muscle spasms, Nausea, Pain, Rash	Not Recovered/ Not Resolved	She had funky hair, she explained that about 3/4 of her hair fell out and when it did grow back, it was tightly wavy (captured as abnormal hair texture) and it would not grow as long. Her eyelashes also grew out of control. They were thin and grew very long. They grew so long that they actually curl back into her eye. She has to either use mascara or trim them to manage them

15	US-ROCHE-1182492 Report from studies United States of America 72 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), Non-small cell lung cancer	Simethicone, Aluminium hydroxide gel, Magnesium hydroxide, Paracetamol, Colecalciferol No past drugs were reported.	Acne, Alopecia, Conjunctivitis Diarrhoea, Disease progression, Eye discharge, Eye irritation, Glossodynia Hair texture abnormal, Lip swelling, Madarosis, Nasal dryness, Pruritus, Rash, Skin burning sensation, Tongue eruption, Weight increased	Dose not changed, Not Recovered/ Not Resolved	Approximately 2-3 months after the dose reduction, her eyelashes started to curl, her eyebrows started to thin and fall out, her hair started to thin, dry.
16	US-ROCHE-1652536 Report from studies United States of America 63 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), Non-small cell lung cancer	Pregabalin nortriptyline, Nortriptyline hydrochloride Simvastatin, Alprazolam, Ezetimibe Past drug therapy: cholesterol	Abdominal pain, Blisters, Dry eye, Gastrooesophageal reflux disease, Hair growth abnormal, Hair texture abnormal, Hypogeusia, Lip pain, Muscle spasms, Oral pain, Rash, Skin ulcer, Taste disorder, Trichiasis, Weight decreased	Drug withdrawn, Not Recovered/ Not Resolved	Eyelashes curling into eye, hair became curly
17	US-ROCHE-1639618 Report from studies United States of America 82 Female Healthcare professional (Physician)	Erlotinib hydrochloride (Tarceva), Lung carcinoma cell type unspecified stage	Alpha-tocopherol, Hydrochlorothiazide levothyroxine, Levothyroxine sodium, Vitamin B12, Denosumab Past drugs were not reported	Alopecia, Arthralgia, Bone loss, Burning sensation, Decreased appetite, Feeding disorder, Hair texture abnormal, Hypophagia, Lip dry, Pruritus, Rash, Urticaria, Weight decreased	Not Recovered/ Not Resolved	Hair became curly, hair fall Later, her hair in the back became curly
18	US-ROCHE-1358451 ROCHE PRODUCTS LIMITED Report from studies United States of America 73 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride (Tarceva), Lung neoplasm malignant	Zolpidem tartrate, Doxycycline hyclate, Omeprazole, Pantoprazol, Pantoprazole sodium, Levothyroxine sodium, Vitamin B12, Cetirizine, Cetirizine dihydrochloride Past drugs were not reported	Acne, Alopecia, Dry eye, Dry skin, Epistaxis, Eructation, Erythema, Eye irritation, Gastrooesophageal reflux disease, Glossitis, Growth of eyelashes, Hair texture abnormal Nasal cavity cancer, Nasal discomfort, Painful respiration, Rash Rhinorrhoea, Skin exfoliation, Stomatitis	Drug withdrawn	She had one eyelash that got real long, almost up to her eyebrow. She lost spots of her hair and it changed texture.
19	US-ROCHE-1962576 Report from studies United States of America 69 Female	Erlotinib hydrochloride (Tarceva), Lung neoplasm malignant	Not reported	Abdominal discomfort, Alopecia Cough, Decreased appetite, Diarrhoea Dyspepsia, Feeding disorder, Hair texture abnormal, Nausea,	Dose not changed, Not Recovered/ Not Resolved	Hair grown back curly

	Healthcare professional (Physician)			Pain of skin, Photosensitivity reaction, Pneumonia, Rash, Weight increased		
20	US-ROCHE-1980487 Report from studies United States of America 73 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride Lung squamous cell carcinoma stage II	Loperamide hydrochloride, Loperamide oxide Radiation (had 36 treatments). No past drugs were reported.	Acne, Acne pustular, Alopecia, Bone disorder, Constipation, Depression, Diarrhoea, Dry eye, Dry skin, Eye disorder, Eye haemorrhage, Eyelash changes, Fatigue, Folliculitis, Hair growth abnormal, Hair texture abnormal, Ill-defined disorder, Impatience, Madarosis, Mass Pneumonia, Rash, Rhinorrhoea, Skin disorder, Skin exfoliation, Urinary tract infection	Not Recovered/ Not Resolved	Two episodes of hair loss Episode of eyelashes growing kinky hair (captured as eyelashes growing kinky hair (straight hair curled)) Lost eyebrows, eyebrows not growing back in the same way (first episode), hair not growing back in the same way (second episode)
21	US-ROCHE-1520276 Report from studies United States of America 65 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride Lung neoplasm malignant	Acetylsalicylic acid, Atorvastatin, Gabapentin, Hydrochlorothiazide, Levothyroxine, Levothyroxine sodium, Losartan potassium, Metoprolol tartrate, Minocycline, Paroxetine hydrochloride, Anhydrous, Simvastatin 3 chemotherapy and 37 radiation treatments (prior to start erlotinib)	Acne, Alopecia, Diarrhoea, Eyelid infection, Eyelid irritation, Eyelid pain, Eyelid rash, Eyelids pruritus, Hair growth abnormal, Hair texture abnormal, Localised infection Malignant neoplasm progression Mass, Nodule, Pruritus, Rash, Rash macular, Sinusitis, Skin disorder, Skin lesion	Drug withdrawn	Hair loss (first occurrence), hair growth on face Hair fell out (second occurrence), hair came back frizzy Later, hair loss resolved. The hair came back, but it was curly and kinky. She experienced hair growth on her face, too.
22	US-ROCHE-1840931 Report from studies United States of America 85 Female Non Healthcare professional (Consumer or other Non-Health Professional)	Erlotinib hydrochloride Lung neoplasm malignant	Amlodipine besylate, Metoprolol succinate No past drugs were reported	Acne Alopecia Cataract, Erythema, Hair colour changes, Hair texture abnormal, Hirsutism, Hypoacusis, Increased appetite, Nail disorder, Peripheral swelling, Rash, Vision blurred	Dose not changed	Her hair loss continued with hirsutism. Hair became darker brown, hair was now curly and cataracts whilst participating in NIP-US-1400
23	US-ROCHE-2075154 Report from studies United States of America 76 Female Non Healthcare professional	Erlotinib hydrochloride (Tarceva), Bone cancer, Lung carcinoma cell type unspecified stage IV, Lung neoplasm malignant	Famotidine, Calcium carbonate, Magnesium hydroxide, Paracetamol Past drugs: penicillin and azithromycin	Alopecia, Decreased appetite, Dry eye, Dry mouth, Dry skin, Dyspnoea, Gastrointestinal disorder, Hair growth abnormal, Hair texture abnormal, Hirsutism,		Eyebrow hairs were growing, episodes of hair on head got curly, dry, kinky and puff and grew hair on nose, above lips and above chin (hirsutism)

	(Consumer or other Non-Health Professional)			Hypoaesthesia, Hypogeusia, Memory impairment, Miliaria, Nasal dryness, Oral disorder, Pruritus, Rash, Stomatitis, Swelling face, Tongue disorder, Visual impairment, Weight decreased		(episode 1 and 2) was episode of losing hair Her eyebrow hairs were growing and the hair on her head got curly (first episode)
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In seven cases (case 2-4, 7-9 and 12), curling of the hair was reported without mentioning other hair problems. In twelve of the twenty-three reports curling of the hair was reported in combination with alopecia (case 1, 11, 14-17 and 17-23), in which in five cases the hair returned curly (case 14 and 18-21). In three cases, curling of the hair was reported in combination with curly eyelashes (case 13, 16 and 18) and in one case with curly eyebrows (case 20). In two cases only curly eyelashes were reported without mentioning curled hair (case 5 and 10). In two other cases (case 7 and 12), onychoclasia (breaking of the finger- or toenails) was reported beside hair texture changes.

In three cases the EGFR mutation was reported (case 8 and 17: deletion T2N2M1 in exon 19 and case 10: Leu858Arg in exon 21). There was one positive dechallenge (case 18). Curly eyelashes recovered after drug withdrawal, however the outcome of the changed hair texture was unknown. Besides erlotinib, case 8 and 11 also received chemotherapy (carboplatin and pemetrexed and Osimertinib), which may have affected the hair structure [11]. In three other cases (case 1, 6 and 21), chemotherapy prior to erlotinib treatment was reported. Considering the long hair cycle (which can take up to years) and the missing latency period for the onset of the adverse reaction in the majority of the cases, affects from previous treatments on the hair cycle could not be excluded.

Prescription data

Table 2. Number of patients using erlotinib (L01EB02) in the Netherlands between 2017 and 2021 [12].

Drug		2017	2018	2019	2020	2021
L01EB02	Erlotinib*	464	471	466	254	123

Erlotinib has been transferred to intramural healthcare as per 01-01-2013, therefore the GIP data is not complete.

Mechanism

EGFR ligands trigger the anagen (growth) and catagen (transition) phases during the hair cycle. Hair follicles of mice with mutations in the EGFR allele failed to enter the catagen phase, resulting in short wavy hair and curling whiskers [4]. Eventually this can lead to hair follicle degeneration and alopecia.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received a report on changes in hair texture following erlotinib treatment. The official product information of erlotinib mentions *alopecia, change in eyebrow, hirsutism and eyelash changes*, however *changes in hair texture* other than the eyelashes is not mentioned. Additionally to the report received by Lareb, hair texture changes were reported 57 times in Eudravigilance, of which 23 cases were on curling hair and/or curling or lengthening of the eyelashes and eyebrows. Of these, 11 reports were spontaneously reported and 12 were from American studies. There was one positive dechallenge. Since erlotinib is indicated as first line therapy in non-small cell lung carcinoma, as well as maintenance treatment for patients with stable disease after first-line chemotherapy, affects from previous treatments could not be excluded. However, case-reports and a possible mechanism add to the likelihood of the association of EGFR inhibitors and changes in hair texture. Hence, a causal relationship is considered plausible.

References

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This signal has been raised on May 23, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl