Two Cases of Psoriasis Responding to Erlotinib: Time to Revisiting Inhibition of Epidermal Growth Factor Receptor in Psoriasis Therapy?

Tobias R. Overbeck  Frank Griesinger
Hematology and Oncology, University Medicine Göttingen, Göttingen, and Hematology and Oncology, Pius Hospital Oldenburg, Oldenburg, Germany

Abstract
Erlotinib inhibits the tyrosine kinase of epidermal growth factor receptor (EGFR) and is successfully used in lung cancer treatment. EGFR is essential in skin development and function and may have a role in the pathogenesis of psoriasis. Cutaneous side effects are very common in patients treated with erlotinib, therefore erlotinib has not been considered for the treatment of dermatological disorders. In the current report, we demonstrate a prolonged positive effect of erlotinib on psoriasis in 2 patients.

Case Reports

Patient 1
In 1998, a 58-year-old Caucasian female patient underwent R0 resection of non-small cell lung cancer (bronchioloalveolar carcinoma, EGFR mutation status unknown) of the left lower lobe at stage IB with no further adjuvant therapy. After about 14 days on erlotinib 150 mg/day, nausea and rash of both hands, feet, lower legs and abdomen started. On day 21 after starting oral erlotinib treatment 150 mg/day, she presented at our Outpatient Clinic. Cough and dyspnea were treated successfully. Due to a rash (maximum grade II) of the lower limbs, erlotinib was reduced from 150 to 100 mg/day. Erlotinib treatment was continued for 9 months until the death of the patient due to disease progression.

The patient had suffered from psoriasis since her childhood. A positive family history was noted as her father was also affected by the disease. Diverse local treatments since her childhood had provided partial and temporary relief. In 1998, the patient presented as an outpatient in a dermatological department with a reddened and desquamating plaque in the lumbar area as well as with typical psoriatic manifestations at her dorsal elbow area. Balneophototherapy in combination with UVA/UVB irradiation was started leading to a near complete remission of the described psoriasis manifestations. Consolidation therapy was given with calcipotriol ointment and local corticosteroids. Persisting lumbar plaque was further treated with keratolytic as well as with calcipotriol ointment, leading to a partial remission. Relapse was noted in 2000, again with lumbar plaque as the leading manifestation. At this time, local therapy with betamethasone, leukichthol, zinc oxide in unguentum emulsificans aquosum alternat-

Key Words
Epidermal growth factor receptors · Erlotinib · Lung cancer · Psoriasis · Tyrosine kinase inhibitors

Introduction

Erlotinib inhibits the tyrosine kinase of epidermal growth factor receptor (EGFR) and is successfully used in lung cancer treatment. EGFR is essential in skin development and function and may be involved in the pathogenesis of psoriasis due to EGFR-mediated hyperstimulation. Cutaneous side effects are very common in patients treated with erlotinib, therefore erlotinib has not been considered for the treatment of dermatological disorders. In the current report, we demonstrate a prolonged positive effect of erlotinib on psoriasis in 2 patients.
ing with salicyl-vaseline again resulted in a partial remission. Since 2000, no further specific therapy of psoriasis was given.

Non-inflammatory and non-pruriginous psoriasis persisted at first presentation in our Oncology Department and before starting therapy with erlotinib in July 2005. Again, the leading manifestation was the lumbar plaque, as well as lesions at her dorsal elbow area and ventral sites of her distal lower limbs. After 3 weeks of treatment with erlotinib, psoriatic manifestations had completely resolved. There was no recurrence of psoriasis during treatment with erlotinib for 9 months until death.

**Patient 2**
The 2nd case was a 66-year-old Caucasian male patient with squamous non-small cell lung cancer at stage IIIB diagnosed in 2006. EGFR mutation was verified retrospectively (P694L point mutation, exon 18). The patient was treated with erlotinib in a neoadjuvant setting for 6 weeks and subsequently received adjuvant therapy for 12 months. During the neoadjuvant course, psoriasis which was first diagnosed 11 years ago resolved after about 14 days on erlotinib but then relapsed during the erlotinib-free 7-month interval. Due to rash of grade II, erlotinib had to be reduced from 150 to 100 mg in the adjuvant course and again psoriatic lesions resolved after about 14 days on erlotinib. Having completed adjuvant therapy with erlotinib for 12 months, no recurrence of psoriasis was observed for further 27 months until death due to recurrent lung cancer in 2010.

**Discussion**

EGFR is important for normal skin development and function. It is expressed in keratinocytes in the basal and in psoriatic skin with higher levels in the first suprabasal layers [1, 2]. In psoriasis, the balance of signals that regulate the homeostasis of normal epidermis is altered [3]. It has been hypothesized that intrinsic alterations in keratinocytes, or local or general immune disorders could be involved [4, 5]. The causal abnormality could be the result of an increased recruitment of cycling cells from the resting fractions. Inappropriate survival of keratinocytes due to EGFR-mediated hyperstimulation is thought to contribute to the pathogenesis of psoriasis [5, 6]. In psoriasis and other hyperproliferative skin conditions, EGFRs are persistently expressed throughout the interfollicular epidermis as long as the growth-stimulatory signal persists. One of the first biochemical signs of effective therapy of psoriasis is the return of the EGFR pattern toward the primarily basilar distribution seen in normal human adult skin [6]. Complete resolution of psoriasis in our patients treated with erlotinib for lung cancer may have resulted from its EGFR-controlling effect of the cell cycle of keratinocytes abnormally stimulated by psoriasis [4, 7].

The first report that a therapeutic modality in psoriasis treatment affects EGFR was published in 1989: psoralen/ultraviolet A therapy specifically caused a dramatic decrease in EGF-induced EGFR activity in A431 cells. This effect was thought to be mediated by a rapid increase in phosphate content of EGFR at serine residues [8].

Recently, before the era of EGFR inhibitors like gefitinib and erlotinib, a variety of tyrophostins known to inhibit receptor tyrosine kinases including EGFR were shown to inhibit psoriatic keratinocyte proliferation in vitro and this effect correlated with the inhibition of EGFR activity [7, 9]. Varani et al. [10] established serum and growth-factor-free cultures from psoriatic lesional as well as normal skin. Normal skin plus growth-factor-enriched culture medium exhibited a psoriatic-like appearance. Lesional skin continued to express features of psoriatic plaques, but in the presence of an antibody to EGF the abnormal histological features of the psoriatic tissue were partially ameliorated. These data suggest that growth factors which act through EGFR help to maintain the psoriatic phenotype in organ culture and could be inhibited by antibodies.

The first report of EGFR inhibition having a positive effect on psoriasis was in a patient with long-standing psoriasis receiving cetuximab (an EGFR antibody) and chemotherapy for lung cancer. The antineoplastic therapy led to a significant improvement in psoriasis; however, formally it was not possible to completely rule out that the combination of EGFR blockage and chemotherapy was necessary for this effect [4]. Of note is that the patient developed the typical EGFR inhibitor side effects such as acneiform exanthema of the skin.

The second report was in a patient with lung cancer and long-standing psoriasis receiving gefitinib for lung cancer. In this patient, psoriasis deteriorated significantly and even arthritis occurred. The authors concede that this observation cannot be interpreted based on the data available in the literature; of note, no information on the side effects of gefitinib concerning acneiform exanthema are given [11].

Giroux et al. [12] reported the case of a man with lung cancer and psoriasis with response of the skin lesions to erlotinib 3 months after the beginning of erlotinib and remission for at least 2 months. As in the current presentation, erlotinib had to be reduced due to the occurrence of rash.

Narayanan et al. [13] reported the case of a man with renal cancer who had psoriasis. He was first treated with erlotinib for 3 months and experienced toxicity to the skin (rash). Due to progression of renal cancer, erlotinib was stopped. The authors did not report any effect on psoriasis during erlotinib treatment. One year later, the patient was put on sunitinib, an inhibitor targeting multiple tyrosine kinases including receptors for platelet-derived growth factor α and β (PDGFR) and vascular endothelial growth factor receptors (VEGFR). During treatment with sunitinib, the patient noted improvement in psoriasis. During the off-sunitinib interval, the skin of the patient had worsened but improved when sunitinib was restarted again and led to an overall improvement of the skin during the courses. The on-off phenomenon of sunitinib was also reported by Keshtgarpour and Dudek [14].

Sorafenib works by inhibiting VEGFR, PDGFR and Raf-1. Fournier and Tisman [15] reported on a patient with renal cell carcinoma with complete response to sorafenib regarding preexisting psoriasis. In this case, psoriasis recurred after switching tumor therapy to sunitinib. A therapeutic effect of VEGFR tyrosine kinase inhibitors in inflammatory skin disorders such as psoriasis was also postulated by Halin et al. [16].

Long-standing severe psoriasis improved in a patient with metastatic kidney tumor treated with the EGFR and HER2/neu tyrosine kinase inhibitor lapatinib. Total clearance of his psoriasis was observed after a 1-month treatment period with lapatinib who also had typical exanthema as a side effect of tyrosine kinase inhibitor therapy [17].

Furthermore, there is a report about clinical improvement of psoriasis in a patient with metastatic gastrointestinal stro-
mal tumor following therapy with imatinib; no exanthema-like skin toxicity was reported. Imatinib selectively inhibits the abl, c-kit and PDGFR tyrosine kinases [18] and modulates T-cell responses, which plays a major role in the pathogenesis of psoriasis [19]. As no EGFR inhibition is mediated by imatinib, other pathways than EGFR seem to play a role in the maintenance of the psoriatic phenotype.

There is also some preclinical experience with topical application of EGFR inhibitors. In a mouse model of contact hypersensitivity and a single topical administration of a selective EGFR kinase blocker, Mascia et al. [20] observed a markedly enhanced immune response with increased chemokine expression and increased inflammatory cell infiltration.

Disposition studies were conducted in rats and rabbits, using the EGFR tyrosine kinase inhibitor [14C] RG 14620, to investigate percutaneous absorption. Based on dose-adjusted ratios of plasma radioactivity values, the extent of percutaneous absorption appeared to be 1.9% in rats and 0.6% in rabbits, and based on cumulative excretion of radioactivity up to 96 h, percutaneous absorption was 12.0% in the rat and 2.0% in the rabbit [21].

Currently, there are no published data available regarding therapeutic EGFR inhibition in psoriasis arthritis. In the above-cited case report with worsening cutaneous manifestations of psoriasis during therapy with gefitinib, arthritis of the distal interphalangeal joints occurred [11]. This affection of joints during therapy with gefitinib might indicate the activity of EGFR tyrosine kinase inhibitors in this particular field. Table 1 contains a summary of the cited case reports on psoriasis and targeted therapies.

Table 1. Summary of reports about psoriasis and targeted therapies

<table>
<thead>
<tr>
<th>Targeted proteins (selection)</th>
<th>Drugs</th>
<th>Patients</th>
<th>Outcome of psoriasis</th>
<th>Comments</th>
<th>Underlying diseases</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>cetuximab</td>
<td>1</td>
<td>complete remission</td>
<td>no relapse after end of treatment (6-month follow-up), possible bias due to additional chemotherapy</td>
<td>lung cancer</td>
<td>4</td>
</tr>
<tr>
<td>EGFR</td>
<td>gefitinib</td>
<td>1</td>
<td>deterioration</td>
<td>new cutaneous lesions and arthritis</td>
<td>lung cancer</td>
<td>11</td>
</tr>
<tr>
<td>EGFR</td>
<td>erlotinib</td>
<td>1</td>
<td>complete remission</td>
<td>complete remission for at least 2 months</td>
<td>lung cancer</td>
<td>12</td>
</tr>
<tr>
<td>EGFR</td>
<td>erlotinib</td>
<td>2</td>
<td>complete remission</td>
<td>patient 1: complete remission for 9 months patient 2: 1st course (6 weeks with complete remission, relapse during erlotinib-free interval, 2nd course (12 months) with complete remission for 39 months</td>
<td>current case report</td>
<td></td>
</tr>
<tr>
<td>EGFR, HER2/neu</td>
<td>lapatinib</td>
<td>1</td>
<td>complete remission</td>
<td>complete remission for at least 5 months</td>
<td>renal cancer</td>
<td>17</td>
</tr>
<tr>
<td>PDGFR, VEGFR</td>
<td>sunitinib</td>
<td>1</td>
<td>improvement</td>
<td>worsening during off-sunitinib periods (on 4 weeks/ off 2 weeks), overall improvement during 3.5-year treatment period, no effect reported on erlotinib (1st line)</td>
<td>renal cancer</td>
<td>13</td>
</tr>
<tr>
<td>PDGFR, VEGFR</td>
<td>sunitinib</td>
<td>1</td>
<td>improvement</td>
<td>worsening during off-sunitinib periods (on 4 weeks/ off 2 weeks)</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>PDGFR, VEGFR, Raf</td>
<td>sorafenib</td>
<td>1</td>
<td>complete remission</td>
<td>complete remission for at least 3 months, relapse after having switched from sorafenib to sunitinib</td>
<td>renal cancer</td>
<td>15</td>
</tr>
<tr>
<td>abl, c-kit, PDGFR</td>
<td>imatinib</td>
<td>1</td>
<td>improvement</td>
<td>improvement on imatinib (400 mg), worsening at lower dose level (300 mg), further improvement in combination with etretinate</td>
<td>gastrointestinal stromal tumor</td>
<td>18</td>
</tr>
</tbody>
</table>

Conclusion

Our report is in line with the literature suggesting that psoriasis might benefit from EGFR inhibition. Our 2 cases showed for the first time a prolonged effect during and after EGFR inhibition, respectively. In vitro and in vivo data should be generated to confirm the importance of targeted therapy against EGFR in skin disorders. Because of the localized nature of psoriatic skin manifestations, local application of EGFR inhibitors might be beneficial to optimize local improvement and minimize undesirable systemic effects.

Disclosure Statement

The authors have obtained honoraria for lectures and advisory board activities by Roche, and both have participated in clinical trials supported by Roche.

Psoriasis Responding to Erlotinib

References


21 Khetarpal VK, Markham PM, Ziemiaik JA: Dispositional characteristics of a tyrosine kinase inhibitor (RG 14620) in rats and rabbits following intravenous administration or dermal application. Drug Metab Dispos 1994;22:216–223.