Serious Hematologic Complications Following Erlotinib Treatment

G. P. Stathopoulos1, Dim. Trafalis1, A. Athanasiou2, G. Bardí3 and H. Chandrinou1

1First Oncology Clinic, Errikos Dunant Hospital, Athens, Greece;
2Oncology Clinic, Metaxa Hospital, Piraeus, Greece;
3Bio-Analytica Genotype Molecular Cytogenic Laboratory, Athens, Greece

Abstract. Background: Erlotinib is an oral, small-molecule targeting therapy which inhibits epidermal growth factor tyrosine kinase receptors. Erlotinib has been administered for the treatment of advanced pancreatic cancer and non-small cell lung cancer. Patients and Methods: In the present report, unusual hematologic complications were detected after erlotinib was administered as second-line monotherapy in pretreated patients with advanced non-small cell lung cancer. Four patients pre-treated with cisplatin or its analog-based combinations, were evaluated. Erlotinib was given at a dose of 150 mg daily. In cases of intolerable adverse reactions, the dose was either reduced to 100 mg daily or treatment was interrupted for a maximum of two weeks. Results: Serious hematologic toxicity (or complications) developed in these 4 patients after 4-8.5 months of treatment. Two patients developed leukemias (AML, CML) and two, myelodysplastic syndrome. Conclusion: Whether or not these hematologic complications were related to erlotinib treatment is comprehensively discussed.

Erlotinib is an oral, small-molecule targeting therapy which inhibits the epidermal growth factor receptor (EGFR) of tyrosine kinase, blocking signal transduction pathways implicated in the proliferation and survival of cancer cells (1). EGFR is associated with cellular processes leading to tumorigenesis (2, 3). Data exist concerning erlotinib administration for malignant tumors, mainly pancreatic cancer, in combination with another cytotoxic agent and also for non-small cell lung cancer (NSCLC) in a large number of patients as second-line treatment (4). Erlotinib has provided a survival benefit for advanced NSCLC patients (5, 6). Survival benefit was even shown in several subsets of NSCLC patients such as patients with squamous cell carcinoma, smokers and males, where gefitinib did not appear to be active (5).

Serious adverse reactions are uncommon. The most common side-effects are skin rash and serious grade 3-4 anorexia and then fatigue, vomiting and stomatitis which were reported to be <1%. Grade 3-4 diarrhea was also <1% (6).

The present report involves erlotinib monotherapy in pretreated patients with advanced NSCLC.

Case Reports

Case 1. A 67-year-old male patient was histologically diagnosed with inoperable, stage IIIB adenocarcinoma, with pleura infiltration and pleura infusion. This patient was treated with cisplatin 80 mg/m²-gemcitabine 1 gr/m² chemotherapy for six cycles. He achieved a partial response for a duration of six months. On disease progression 11 months after the beginning of chemotherapy, the patient was given erlotinib treatment (150 mg daily, for 4 months). This treatment was discontinued due to grade 4 thrombocytopenia. The bone marrow showed the megakaryocytes slightly reduced and no infiltration by abnormal cells was detected. The thrombocytopenia lasted for 4 months. A new bone marrow aspiration was performed and myelodysplastic syndrome was confirmed. In all of the mitoses, deletion of the lung arm of chromosome 20 from the band 20q11 till 20qter was found. The karyotype of the sample was 46,XY,del(20)(q11)[15]/47,idem,+21(7)/48,idem,21,+21[-3].

Case 2. A 70-year-old male patient was histologically diagnosed with inoperable, stage IIIB adenocarcinoma of the lungs. He was treated with cisplatin 80 mg/m² combined with paclitaxel 175 mg/m² for 6 cycles and achieved a partial response for 4 months. As second-line treatment, he was given erlotinib 150 mg daily, for 8 months; the patient had a partial response. The blood white cell count (WBC) increased to 92,000/μl. By discontinuing erlotinib the WBC dropped slightly to 82,000/μl. Analytically, the white cells were: 28% myelocytes, 4% promyelocytes, 8% metamyelocytes and 50% neutrophils. Believing that by discontinuing erlotinib, the
abnormal WBC count might be reduced, we waited for 3 weeks but the count remained the same. The analysis of the DNA isolated by the bone marrow did not detect the V617F mutation in the JAK2 gene. However, the cells expressed the BCR-ABL fusion transcript. The level of expression was estimated by RT real-time PCR. The ratio of BCR-ABL mRNA level to GAPDH mRNA was $2 \times 10^{-2}$.

Case 3. A 60-year-old female was histologically diagnosed with inoperable, stage IIIB adenocarcinoma of the lung, in September 2004. As primary treatment, she received 3 cycles of chemotherapy with cisplatin 80 mg/m² + vinorelbine 25 mg/m²; radiotherapy (RT) of the primary lung lesions and of the mediastinum followed and the treatment was completed with 3 more cycles of cisplatin 80 mg/m² + vinorelbine 25 mg/m² chemotherapy. The primary treatment resulted in a partial response, with a duration of 10 months until disease progression. Another partial response was achieved with second-line therapy of 3 cycles of carboplatin 6 AUC + etoposide 120 mg/m² chemotherapy but this was discontinued because of severe hematologic toxicity (leukopenia). The second partial remission lasted 5 months. After tumor progression, the patient was given erlotinib, 150 mg daily, and the disease remained stable for 5.5 months, until the patient was admitted to hospital for further clinical and laboratory evaluation because of anemia (Hct 25.7%) and leucopenia (3.200 WBCs/μl). Hematological tests revealed 14% myeloblasts in the bone marrow aspiration and cytogenetic tests showed clonal abnormalities in 12/20 of the analyzed metaphases of bone marrow blast cells with karyotype: 47,XX,+8, t(5;9)(q13;q34) and the diagnosis of myelodysplastic syndrome (MDS), RAEB, was made. The patient continued to receive erlotinib treatment despite the tumor progression, as well as best supportive care. She died of respiratory failure due to lung cancer progression, 8.0 months later. The MDS appeared 14 months after chemotherapy (Table I shows the data for the aforementioned four patients).

Discussion

One of the first growth factors discovered was epidermal growth factor (EGF) (7). It is a protein which binds to a cell surface growth factor receptor, the EGFR. In the binding to the receptor, EGF either induces cell proliferation or differentiation in mammalian cells (8).

The binding of a ligand to the EGFR induces conformational changes within the receptor which increases the catalytic activity of its intrinsic tyrosine kinase, resulting in autophosphorylation which is necessary for biological activity (9, 10). Protein tyrosine kinase activity plays a key role in the regulation of cell proliferation and differentiation (11). A large number of deletions of the EGFR have been observed in a number of neoplasias such as glioblastoma in NSCLC, breast cancer, pediatric gliomas, medulloblastomas and ovarian carcinomas (11). Overexpression of mRNA and/or protein encoded by the EGFR gene has been observed

---

Table I. Patients with hematologic neoplasias after erlotinib treatment.

<table>
<thead>
<tr>
<th>Case</th>
<th>Histology</th>
<th>Duration of erlotinib treatment</th>
<th>Blood test results</th>
<th>Time after first-line chemotherapy</th>
<th>Bone marrow</th>
<th>Diagnosis</th>
<th>Prior treatment</th>
<th>Blood test results</th>
<th>Time after first-line chemotherapy</th>
<th>Bone marrow</th>
<th>Diagnosis</th>
<th>Prior treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adenocarcinoma</td>
<td>4 months</td>
<td>Grade 4 thrombocytopenia</td>
<td>11 months</td>
<td>Low megakaryocytes</td>
<td>MDS</td>
<td>CDDPb-Gemcitabine</td>
<td>Grade 4 thrombocytopenia</td>
<td>11 months</td>
<td>Low megakaryocytes</td>
<td>MDS</td>
<td>CDDPb-Gemcitabine</td>
</tr>
<tr>
<td>2</td>
<td>Adenocarcinoma</td>
<td>8 months</td>
<td>Leukocytosis</td>
<td>12 months</td>
<td>BCR-ABL+</td>
<td>CML</td>
<td>CDDP-Paclitaxel</td>
<td>Leukocytosis</td>
<td>12 months</td>
<td>BCR-ABL+</td>
<td>CML</td>
<td>CDDP-Paclitaxel</td>
</tr>
<tr>
<td>3</td>
<td>Adenocarcinoma</td>
<td>8.5 months</td>
<td>Pancytopenia</td>
<td>36 months</td>
<td>23% Myeloblasts</td>
<td>AML</td>
<td>VRL4-CDDP XRTe</td>
<td>Pancytopenia</td>
<td>36 months</td>
<td>23% Myeloblasts</td>
<td>AML</td>
<td>VRL4-CDDP XRTe</td>
</tr>
<tr>
<td>4</td>
<td>Squamous cell cancer</td>
<td>4.5 months</td>
<td>Anemia</td>
<td>14 months</td>
<td>14% Myeloblasts</td>
<td>MDS RAEBa</td>
<td>Carbo-etopside</td>
<td>Anemia</td>
<td>14 months</td>
<td>14% Myeloblasts</td>
<td>MDS RAEBa</td>
<td>Carbo-etopside</td>
</tr>
</tbody>
</table>

aRefractory anemia with excess blasts; bicisplatin; ccarboplatin; dvinorelbine; e radiation therapy.
in many types of human malignancies (12) including breast (13), gastric, colorectal (14) and bladder cancer (15). In NSCLC, EGFR expression at percentages varying from 30%-70%, has been reported (16, 17). Erlotinib is an anti-EGFR targeting agent; studies have already been performed and reports concerning its value have been documented (18, 19). However, despite the fact that targeting therapy has been administered in quite a number of clinical trials over recent years, there are many unanswered questions related to the failure to achieve the expected success and to explain certain adverse reactions or complications. Tumors are likely to express variable but excessive numbers of HER1/EGFRs. Unless all receptors are effectively inhibited from initiating signaling, there is likely to be sufficient residual tumorigenic activity to maintain disease (20). Evidence, although unconfirmed, suggests that cancers become dependent on one or more specific elements of the cell signaling circuit, requiring their continued presence in order to remain malignant (21).

In the 4 patients described above, after 4-8 months on erlotinib treatment, myeloid neoplasms were detected: one acute myeloblastic leukemia (AML), one chronic myeloid leukemia and two patients with myelodysplastic syndrome. The karyotype examination showed abnormalities in 3 out of the 4 patients. Whether or not these hematologic lesions can be attributed to erlotinib treatment is questionable. There have been a few articles related to leukemia and anti-EGFR agents. In one, erlotinib was administered to a patient who had concurrent NSCLC and AML. No chemotherapy was given. It was observed that within 3 months there was a myeloblast reduction (22). Another article suggested that erlotinib induces differentiation, cell-cycle arrest and apoptosis of EGFR-negative myeloblasts in patients with myelodysplastic syndrome (MDS) and AML as well as EGFR-negative cell lines representing these diseases (23). Another case report indicated that erlotinib produced complete remission in a patient with AML (24). The common factor between the aforementioned cases and ours is that all of these 4 patients had leukemias (acute or chronic) and myelodysplastic syndrome. The difference is that in the aforementioned patients erlotinib was effective for leukemias with EGFR-negative expression. Our patients were on treatment with erlotinib when the diagnosis of hematologic malignancies was made. One of our patients with AML continued treatment with erlotinib without response and passed away some months later. Leukemogenesis may have been due to the previous chemotherapy treatment. The agents we used, cisplatin or its analogs and paclitaxel, docetaxel and gemcitabine, have not been related to a second primary malignancy development. Of the agents used in our study, only etoposide has been related to a second primary malignancy. The time period between the first treatment and a leukemia diagnosis varied from 4-20 months, which is a short period of time for a second primary malignancy to develop. It has been indicated that the leukemia pre-existed and the chemotherapy and eventually the anti-EGFR targeting therapy, suppressed the proliferation of leukemic cells to such an extent that the diagnosis of leukemia was obscured (25). Gefitinib, another anti-EGFR agent, has also been observed to be related to leukemia. Gefitinib has been administered for NSCLC and during the treatment, leukemia developed (26, 27).

Erlotinib may be an eligible second-line treatment for NSCLC patients. The great majority of patients tolerate the treatment and adverse reactions. Our observations suggest that erlotinib treatment may induce myeloid neoplasms. To our knowledge, this is the first report of four cases that developed myeloid neoplasms while on erlotinib treatment.

References


