Serious Hematologic Complications Following Erlotinib Treatment

G.P. STATHOPOULOS[1], DIM. TRAFALIS[1], A. ATHANASIOU[2], G. BARDI[3] and H. CHANDRINOU[1]

[1]*First Oncology Clinic, Errikos Dunant Hospital, Athens, Greece;*
[2]*Oncology Clinic, Metaxa Hospital, Piraeus, Greece;*
[3]*Bio-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/m^2-gemcitabine 1 gr/m^2 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/m^2 combined with paclitaxel 175 mg/m^2 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/μ/l. By discontinuing erlotinib the WBC dropped slightly to 82,000/μ/l. Analytically, the white cells were: 28% myelocytes, 4% promyelocytes, 8% metamyelocytes and 50% neutrophils. Believing that by discontinuing erlotinib, the

Correspondence to: G.P. Stathopoulos, MD, Semitelou 2A, 115 28 Athens, Greece. Tel: +30 2107752600, Fax: +30 2107251736, e-mail: dr-gps@ath.forthnet.gr

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Table I. *Patients with hematologic neoplasias after erlotinib treatment.*

Case	1	2	3	4
Histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Squamous cell cancer
Duration of erlotinib treatment	4 months	8 months	8.5 months	4.5 months
Blood test results	Grade 4 thrombocytopenia	Leukocytosis	Pancytopenia	Anemia
Time after first-line chemotherapy	11 months	12 months	36 months	14 months
Bone marrow	Low megakaryocytes	BCR-ABL+	23% Myeloblasts	14% Myeloblasts
Diagnosis	MDS	CML	AML	MDS RAEB[a]
Prior treatment	CDDP[b]-Gemcitabine	CDDP-Paclitaxel	VRL[d]-CDDP XRt[e] Carbo-etoposide	Carbo[c]-etoposide

[a]Refractory anemia with excess blasts; [b]cisplatin; [c]carboplatin; [d]vinorelbine; [e]radiation therapy.

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 2×10^{-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/m^2 + vinorelbine 25 mg/m^2; 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/m^2 + vinorelbine 25 mg/m^2 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/m^2 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 8.5 months, until the patient was admitted to hospital because of fever (38.6˚C), anemia (Hct 28.8%), leukopenia (2,500 WBCs/μl) and thrombocytopenia (72,000 PLTs/μl). Hematological tests revealed 23% myeloblasts in the bone marrow aspiration and cytogenetic tests showed clonal abnormalities in 9/11 of the analyzed metaphases of bone marrow blast cells with karyotype: 46,XX,del(7)(q22), add(21)(q22), and the diagnosis of myelodysplastic syndrome (MDS), RAEB-T/t-AML, was confirmed. The patient was treated with best supportive care and died due to pneumonia 3.5 months later in a regional hospital.

Case 4. A 59-year-old female was histologically diagnosed with inoperable, stage IV squamous cell carcinoma of the lung in July 2007. As primary treatment, she received 6 cycles of carboplatin 6 AUC + etoposide 120 mg/m^2 chemotherapy. This primary treatment resulted in disease stability, which lasted for 8 months until disease progression. After tumor progression, the patient received second-line treatment with 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

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

1 Baselga J and Arteaga CL: Critical update and emerging trends in epidermal growth factor receptor targeting in cancer. J Clin Oncol *23*: 2445-2459, 2005.

2 Jänne PA, Engelman JA and Johnson BE: Epidermal growth factor receptor mutations in non-small-cell lung cancer: implications for treatment and tumor biology. J Clin Oncol *23*: 3227-3234, 2005.

3 Swinson DE, Cox G and O' Byrne KJ: Coexpression of epidermal growth factor receptor with related factors is associated with poor prognosis in non-small cell lung cancer. Br J Cancer *91(7)*: 1301-1307, 2004.

4 Comis RL: The current situation: erlotinib (tarceva) and gefitinib (iressa) in non-small cell lung cancer. The Oncologist *10*: 467-470, 2005.

5 Byoung Chul-Cho, Chong-Kun Im, Moo-Suk Park *et al*: Phase II study of erlotinib in advanced non-small cell lung cancer after failure of gefitinib. J Clin Oncol *25*: 2528-2533, 2007.

6 Shepherd FA, Pereira JR, Ciuleanu T *et al*: Erlotinib in previously treated non-small cell lung cancer. N Engl J Med *353*: 123-132, 2005.

7 Cohen S: The epidermal growth factor (EGF). Cancer *51*: 1787-1791, 1983.

8 Yarolen Y and Schlessinger J: Epidermal growth factor induces rapid reversible aggregation of the purified epidermal growth factor receptor. Biochemistry *26*: 1443-1451, 1987.

9 Hsuan JJ: Oncogene regulation by growth factors. Anticancer Res *13*: 2521-2522, 1993.

10 Soler C, Beguinot L and Carpenter G: Individual epidermal growth factor receptor autophosphorylation sites do not stringently define association motifs for several SH-2 containing proteins. J Biol Chem *269*: 12320-12324, 1994.

11 Voldborg RB, Damstrup L, Spang-Thomsen M *et al*: Epidermal growth factor receptor (EGFR) and *EGFR* mutations, function and possible role in clinical trials. Ann Oncol *8*: 1197-1206, 1997.

12 Jin-Hee Ann, Sang-We Kim, Seung-Mo Hong *et al*: Epidermal growth factor receptor (EGFR) expression in operable non-small cell lung carcinoma. J Korean Med Sci *19*: 529-535, 2004.

13 Sainsbury JRC, Nicholson S, Angus B *et al*: Epidermal growth factor receptor status of histological sub-types of breast cancer. Br J Cancer *58*: 458-460, 1988.

14 Yasui W, Sumiyoshi H, Hata J *et al*: Expression of epidermal growth factor receptor in human gastric and colonic carcinomas. Cancer Res *48*: 137-141, 1988.
15 Smith K, Fenelly JA, Neal DE *et al*: Characterization and quantitation of the epidermal growth factor receptor in invasive and superficial bladder tumors. Cancer Res *49*: 5810-5815, 1989.
16 Veale D, Kerr N, Gibson GJ *et al*: Characterization of epidermal growth factor receptor in primary human non-small cell lung cancer. Cancer Res *49*: 1313-1317, 1989.
17 Fujino S, Enokibori T, Tezuka N *et al*: A comparison of epidermal growth factor receptor levels and other prognostic parameters in non-small cell lung cancer. Eur J Cancer *32A*: 2070-2074, 1996.
18 Hortobagyi GN and Santer G: Challenges and opportunities for erlotinib (tarceva). What does the future hold? Semin Oncol *30(suppl 7)*: 47-53, 2003.
19 Arteaga CL: The epidermal growth factor receptor: from mutant oncogene in nonhuman cancers to therapeutic target in human neoplasias. J Clin Oncol *19(suppl)*: 32S-40S, 2001.
20 Perez-Soler R: HER1/EGFR Targeting: Refining the strategy. The Oncologist *9*: 58-67, 2004.
21 Weinstein IB: Addiction to oncogenes – the Achilles heal of cancer. Science *297*: 63-64, 2002.
22 Crino L, Eberhardt W, Boyer M *et al*: Erlotinib as second-line therapy in patients (PTS) with advanced non-small-cell lung cancer (NSCLC) and good performance status: interim analyses from the TRUST Study. Abstract Book 33rd ESMO Congress *Suppl 8*: 264, 2008.
23 Groen H, Barata F, McDermott R *et al*: Efficacy of erlotinib in >4000 patients (PTS) with advanced non-small cell lung cancer (NSCLC): Analysis of the European Subpopulation on the TRUST Study. Abstract Book 33rd ESMO Congress *Suppl 8*: 266, 2008.
24 Chan G and Pilichowska M: Complete remission in a patient with acute myelogenous leukemia treated with erlotinib for non-small-cell lung cancer. Blood *110*: 1079-1080, 2007.
25 Hotta K, Kiura K and Takigawa N: Paradoxical clinical effects of epidermal growth factor receptor – tyrosine kinase inhibitors for acute myelogenous leukemia. J Clin Oncol *26*: 5826-5827, 2008.
26 Uchida A, Matsuo K and Tanimoto M: APL during gefitinib treatment for non-small cell lung cancer. N Engl J Med *352*: 842-843, 2005.
27 Ennishi D, Sezaki N and Senoo T: A case of acute promyelocytic leukemia during gefitinib treatment. Int J Hematol *84*: 284-285, 2006.

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