Gefitinib (Iressa, ZD 1839) A Potential Chemotherapy Sensitizer in Previously Chemotherapy Nonresponded Advanced Non-Small-Cell Lung Cancer Patients

Sir,

The standard treatment for patients with advanced or metastatic non-small-cell lung cancer (NSCLC) is a platinum-based combination chemotherapy. Usually after platinum-based therapy failure the second line chemotherapy with docetaxel has been shown to have modest benefit. Treatment options for patients unable to tolerate chemotherapy or failing second line chemotherapy are limited.

On May 5, 2003, gefinitib (Iressa; ZD1839) 250-mg tablets (AstraZeneca Inc.) received accelerated approval by the United States Food and Drug Administration as monotherapy for patients with locally advanced or metastatic non-small cell lung cancer after failure of both platinum-based docetaxel chemotherapies.

We report here our observation of the gefinitibe (Iressa) induced chemo-sensitization and response in previously chemotherapy non-responded advanced non-small cell lung cancer patients.

Case 1. A 48–year-old woman with locally-advanced NSCLC of squamous cell type was treated with combination chemotherapy consisting of paclitaxel (175mg/m^2) and carboplatin (5AUC) till September, 2000. In March 2001, tumour progression was observed. The patient did not respond to second line treatment using docetaxel (75mg/m^2), but responded to gefitinib (250mg/d) which was given from January 2002 to March 2004. In March 2004, pericardial effusion and massive mediastinal lymphadenopathy developed and she underwent pericardiotomy. In April 2004 the patient received single-agent, biweekly-vinorelbine (30mg/m^2) with prompt response. She died after a 12-week course of treatment as a result of an acute event of mesenteric artery thrombosis diagnosed by clinical presentation and CAT scan, while in remission.

Case 2: A 50-year-old woman with metastatic NSCLC of adenocarcinoma type, received combination chemotherapy using gemcitabine (1000mg/m^2) and cisplatin (75mg/m^2) in March 2001 with partial response. In December 2002, because of tumour progression, the patient was sequentially treated with docetaxel (75mg/m^2) and gefitinib(250mg/d) with no apparent response. In January 2004, the patient developed

pericardial and bilateral pleural effusions and underwent pericardiocentesis. Treatment with single-agent, weekly-carboplatin (AUC-2) showed prompt response and resolution of lung lesions and effusions. Response lasted for 5 months.

COMMENTS :

The potentiation of the antitumour activity of cytotoxic drugs by interfering with EGFR activation may have important clinical implications. In fact, it has been proposed that it is possible to enhance anticancer activity by treatment with maximum tolerated doses of cytotoxic drugs in combination with signal transduction inhibitors instead of increasing chemotherapy doses to supertoxic levels that require complex medical support, including hematopoietic rescue.[1] In this respect, the feasibility and antitumour activity of the combined treatment of cisplatin and MAb C225 in patients with advanced head and neck or lung carcinomas has been demonstrated.[2] Similarly, blockade of c-*erb*B-2 signaling by treatment with a recombinant humanized anti-c-*erb*B-2 MAb (Herceptin) enhances the antitumour activity of cisplatin in metastatic breast cancer patients.[3] Furthermore, a randomized Phase III trial has recently demonstrated that the addition of Herceptin in advanced breast cancer patients treated with paclitaxel or doxorubicin increases the activity of chemotherapy alone.[4] A series of experiments was performed to evaluate the potential combined antiproliferative effect of treatment with ZD-1839 and a wide variety of cytotoxic drugs with different mechanism(s) of action that are currently used in the treatment of human epithelial cancers. The effects on the anchorage-independent growth of all four cancer cell lines of three different platinum-derived compounds (cisplatin, carboplatin, and oxaliplatin), two taxanes (paclitaxel and docetaxel), two topoisomerase II inhibitors (doxorubicin and etoposide), a topoisomerase I inhibitor (topotecan), and a thymidylate synthase inhibitor (raltitrexed) were tested in combination with the EGFR tyrosine kinase inhibitor ZD-1839.[5] Fujiwara et al[6] described four cases of patients with advanced NSCLC who previously responded to gefitinib and obtained significant tumour regression through retreatment with other cytotoxic agents. Gefitinib might restore chemosensitivity to previously chemorefractory patients. Our observation is random but reasonable, we feel an experimental study using ZD-1839 (Iressa) followed by combination chemotherapy may be worth exploring.

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