

Safety of pregnancy following breast cancer

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To the Editor

We appreciate the comments by Peccatori and Azim regarding our recent publication [1] in *Acta Oncologica*. We agree with their fundamental point. A subsequent full term pregnancy may well have a beneficial effect on the risk of relapse in patients with early breast cancer. For several reasons we however up-front decided not to perform the subgroup analysis analyses on hormone receptor status that Peccatori and Azim are suggesting. First of all the power of subgroup analysis would be small even in this large cohort, secondly shifting methodologies have been used for oestrogen and progesterone receptor measurements over the more than two decades [2].

The relative importance of pregnancy associated hormonal changes is not fully understood, e.g., the role of prolactin and insulin and other receptors e.g. the insulin-like growth factor I receptor may be important [3,4]. Based on our incomplete understanding of a possible "biological" effect and a genuine concern regarding the risk of selection bias we want to avoid the promotion of pregnancy as therapeutic measure in breast cancer patients.

Furthermore, it is important to bear in mind, that the risk estimates tells us about differences in survival between groups of women with breast cancer. Women with a history of breast cancer will overall still have an increased risk of death compared with other healthy mothers. The present study only indicates that a pregnancy after treatment for breast cancer has no negative impact on the prognosis.

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A case of advanced non-small-cell lung cancer who responded slowly to gefitinib monotherapy after long-term disease stabilization

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To the Editor

The epidermal growth factor receptor (EGFR) is a promising target for anticancer therapy because it is

expressed in a variety of tumors including non-small-cell lung cancer (NSCLC), and elevation of serum levels of EGFR expression has been associated with

a poor prognosis. Gefitinib is an orally active anilinoquinazoline compound which inhibits EGFR tyrosine kinase activity. Previous studies of the gefitinib monotherapy for NSCLC patients showed a significant antitumor activity with the response rate of around 20% and acceptable toxicities even for elderly patients [1–5]. Recently, *EGFR*-mutant tumors were found to yield a high sensitivity to gefitinib as observed in preclinical and clinical studies [6,7]. Surprisingly, most responders to gefitinib monotherapy showed rapid tumor regression, with 68% meeting the criteria for objective response by the first postbaseline assessment and the remaining patients met the criteria in the second, third, or fourth month following randomization [8]. Indeed, there have been no reports showing an objective response to gefitinib after long-term treatment. In this report, we showed a case of advanced NSCLC in whom a partial response to gefitinib was finally identified 14 months after achieving disease stabilization.

Case report

A 76-year-old woman was referred to our department in November 2002 because of an abnormal chest shadow (Figure 1A) and was diagnosed with stage IV adenocarcinoma of the lung (T1N2M1) with pulmonary metastasis. The mutation analysis by enriched polymerase chain reaction method revealed that the tumor possessed the deletion mutation in the exon 19 of *EGFR* gene. Treatment with gefitinib 250 mg/day was initiated in January 2003 as first-line therapy because she was considered unfit for platinum-based chemotherapy. The patient obtained stable disease (20% regression) as

an overall response 2 months after the start of gefitinib treatment, as defined by standard Response Evaluation Criteria In Solid Tumors (RECIST) guidelines (Figure 1B). The patient continued to receive gefitinib because of this favorable disease control coupled with symptom improvement and the absence of severe adverse events. Around January 2003, serum level of carcinoembryonic antigen (CEA) gradually decreased (Figure 2). Unexpectedly, after this reduction in serum CEA level, radiological tumor regression was observed in March 2004, which was defined as a partial response by RECIST (32% regression; Figure 1C). In July 2006, the primary and mediastinal tumors progressed with the elevation of the CEA level with 43.42 ng/ml. The gefitinib treatment was withdrawn and switched to the vinorelbine monotherapy.

Discussion

We experienced a very exceptional case; a partial response was achieved 14 months after the initiation of gefitinib treatment in our patient, in contrast to the majority of responses to gefitinib (250 mg/day), which occurred within the first 4 weeks of treatment [8]. As potential reasons explaining this observation, (i) sensitivity to gefitinib might naturally change over time [9] although no definitive mechanisms were shown so far, and (ii) the tumor might have originally possessed somewhat different biological characters from other NSCLC tumors. Further investigation will be warranted to elucidate the mechanism underlying this phenomenon.

We previously reported that in NSCLC patients obtaining disease stabilization, those who continued gefitinib treatment until disease progression tended

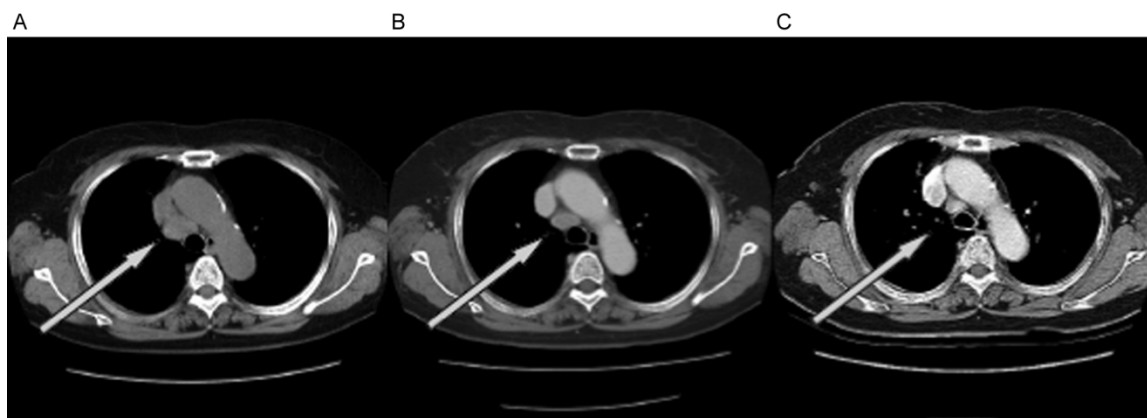


Figure 1. Chest computed tomography scan (A) before treatment of gefitinib, (B) 2 months after treatment and (C) 14 months after treatment. The arrows show the mediastinal lymphnode metastasis that gradually regressed in size.

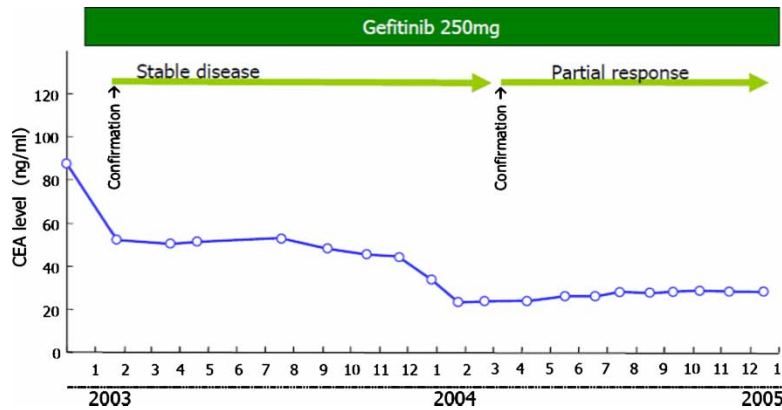


Figure 2. Serial change of serum carcinoembryonic antigen.

to have longer overall and progression-free survival compared with those discontinuing gefitinib treatment (1-year survival rate 52.1% versus 36.6%, $p=0.08$; 1-year progression-free survival rate 31.8% versus 5.2%, $p<0.01$) [5]; the pattern of sensitivity to gefitinib in the case presented here might give us one of the potential clues to understanding of this advantage of the continued gefitinib treatment.

Monitoring of serum tumor marker levels were reported to predict tumor response in previous papers. Massacesi et al. demonstrated that response of serum CEA level to chemotherapy correlated well with subsequent radiological response in patients with metastatic cancer including lung cancer [10]. In our case, the decline of serum CEA level was also observed 2 months before radiological response. Usefulness of tumor markers as predictive factors of tumor response should be reappraised in future studies [11].

In conclusion, this patient obtained an unprecedented response to gefitinib as first-line treatment. It suggests that physicians should be aware of potential objective responses to gefitinib even after the tumor seems to be no more reduced in size with the best overall response of stable disease.

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