A case of long-term survival of gefitinib-induction therapy for advanced N2-multistation lung cancer without epidermal growth factor receptor gene mutation

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Abstract

A 62-year-old female with a productive sputum was pointed out of a mass of 2.5 cm in diameter in left S4 with lymphadenopathy of station 10, 4, and 3 on computed tomographic scan, which were heterogeneously enhanced by radiocontrast agent. She was diagnosed with pulmonary adenocarcinoma and clinical stage IIIA (T1N2M0, N2-multistation). First-line induction therapy of cisplatin plus paclitaxel had been performed but failed to respond to the chemotherapy. Second-line induction therapy of gefitinib for 6 months had showed the shrinkage of the tumor and resulted in a down-stage (T1N0M0, IA). Positron emission topography revealed no abnormal accumulations of the primary tumor and the mediastinal lymph nodes. As salvage surgery, left upper lobectomy was performed and the pathology revealed negative findings of metastasis in lymph nodal station 4, 5, 6, 7, and 11 but in a positive in station 10. The viable cells in the tumor had been residual (Ef.2) and diagnosed with stage IIA (pT1N1M0). Detection test of epidermal growth factor receptor gene mutation showed a negative result. The patient obtained 5-year’s long-term survival without metastasis and recurrence. The combination therapy of gefitinib-induction therapy followed by surgery for advanced lung cancer with N2-multistation would have an advantage of good outcome for such patient in the limited gefitinib-responded population as tailor-made therapies.

Key Words: long-term survival, gefitinib, lung cancer, EGFR-negative

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stage IA (T1N0M0) from stage IIIA (T1N2M0). Left upper lobectomy with nodal dissection was performed in May, 2007. Intraoperative pathology disclosed negative results of lymph node station 3, additional nodal dissection had not been performed. Postoperative pathology showed no metastasis of the dissected lymph nodal station 4, 5, 6, 7, and 11 but the positive of station 10. The shrunk tumor was a 1 cm in diameter (Fig. 3a), but viable cells were observed in the residual tumor (Ef.2) (Fig. 3b). Eventually, she was diagnosed with stage IIA (pT1N1M0). A detection test of EGFR gene mutation showed a negative result. As adjuvant therapy, combination of gemcitabine plus carboplatin was performed in 3 cycles. From September in 2007, as a maintenance therapy, oral administration of S-1 (80 mg in every 1 - 28 days in 6 weeks) had been performed, even though cytotoxic events of diarrhea and elevation of serum bilirubin level, the dose-intensity had to decrease to be 37.5% of...
the initial dosage (40 mg in every 1-14 days in 4 weeks).
We had continued the oral S-1 treatment for 2 years and
completed in September, 2009. The level of CEA was
normal and 1.2 ng/ml in August, 2011. She has been
healthy without recurrence, metastasis, and elevation of
level of CEA value for more than 5 years from the initial
date of the first-line induction therapy for advanced IIIA-
staged lung cancer.

Discussion

Gefitinib is the first targeted drug to be approved for
advanced NSCLC that failed to respond to chemothera-
py. It has a fairly effective antitumor activity in patients
with tumors harboring EGFR gene mutations. However,
the effect of gefitinib as a neoadjuvant therapy remains
unclear, especially unknown in patients without EGFR
gene mutations. In our case, as first-line induction thera-
py, we performed chemotherapy of paclitaxel plus carbo-
platin for the advanced lung cancer with N2-multistation
(T1N2M0, stage IIIA), however, because of the failure in
response of chemotherapy, as second-line induction ther-
apy, oral administration of gefitinib had been performed
for 6 months, the primary tumor and the mediastinal
N2-multistations had been dramatically shrunk. As the
advanced lung cancer had been downstaged, left upper
lobectomy as salvage surgical resection was performed.
The patient could obtain a good five years' long-term
survival from gefitinib-induction therapy followed by
surgery for advanced lung cancer with N2-multistation.

NSCLC patients with specific clinical features appear
to have a greater likelihood of having a mutated form of
EGFR. Analysis of 14 studies involving 2880 patients
showed EGFR mutations occur more frequently in wom-
en than men (38% versus 10%), Asian than non-Asian
patients (32% versus 7%), never-smokers than current or
former smokers (47% versus 7%) and patients with ade-
ocarcinoma histology than non-adenocarcinoma histol-
ogy (30% versus 2%)\(^2\). On the other hand, even though
our case was non-smoker, female, and Asian, the patient
had been expected to response the gefitinib treatment but
had the negative results by a postoperative detection test
of EGFR gene mutation\(^1\). This discrepancy between the
dramatic gefitinib-responder and EGFR gene mutation-
negative result should be caused by the heterogeneity
of the tumor consisting of EGFR mutation-positive and
negative tumor cells. The EGFR-positive cancer cells
might have resulted in apoptosis by gefitinib treatment
and the EGFR-negative ones might have remained as vi-
able cells, or which should be caused by the dependence
on the accuracy of our used detection methods of EGFR
gene mutation\(^1\).

Several prospective clinical trials of gefitinib or erlo-
tinib for treatment of NSCLC patients with EGFR gene
mutations have been done to date\(^3\)-\(^11\). These trials have
shown radiographic response rates ranging from 55% to
82% and a median progression-free survival (PFS) of
8.9 to 13.3 months. These values are three to four times
those historically observed with platinum-based chemo-
therapy as a first-line treatment for advanced NSCLC.
Recently, the role of gefitinib in first-line therapy for pa-
tients with known EGFR mutations was confirmed in the
randomized Phase III Iressa Pan-Asia Study (IPASS)\(^12\).
Gefitinib group demonstrated superior progression-free
survival than carboplatin-paclitaxel group (HR: 0.74;
95% CI: 0.65 – 0.85; P<0.0001) in the overall population.
Most importantly, the PFS of the subgroup of patients with EGFR mutations was significantly better than that of the overall population who received gefitinib alone (HR: 0.48; 95% CI: 0.36 – 0.64; p<0.0001). Patients without EGFR mutations had detrimental effects from treatment with first-line gefitinib (HR: 2.86; 95% CI: 2.05 – 3.86; p<0.0001).

We reviewed on the combination therapy of gefitinib and surgery for advanced lung cancer, some outcomes have been reported; that is, induction therapy of advanced lung cancer harboring EGFR mutation, surgical resection after neoadjuvant gefitinib treatment of lung adenocarcinoma without EGFR mutation, and salvage surgery for advanced NSCLC after response to gefitinib. However, these literatures referred to the results on short- or mid-term outcomes. There were no reports on the long-term outcomes such as our case.

**Conclusion**

We could obtain a successful case of good 5-year’s long-term survival from gefitinib-induction therapy for advanced lung cancer with N2-multistation. A new combination therapy, that is, induction therapy of EGFR-TKI followed by surgery for advanced NSCLC, which would have an advantage of good outcome for such the limited gefitinib-responded patients in EGFR mutation-positive population as tailor-made therapies.

**References**


