Gefitinib for Advanced NSCLC Patients With EGFR Mutation

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Authors' disclosures of potential conflict of interest are found at the end of this article.

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Review of "Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR," by Maemondo et al. (2010). The New England Journal of Medicine, 362(25), 2380–2388. For a discussion of understanding outcomes assessment, please see the related article by Dr. Terri Armstrong on page 48.

Lung cancer continues to be a major threat to our society. It is the number 1 cancer killer, with a mortality rate higher than all common cancers combined (Centers for Disease Control, 2010). Non–small cell lung cancer (NSCLC) is the most common subtype of lung cancer and non–squamous cell carcinoma is the most prevalent histology. Traditionally, with its devastating prognosis and limited treatment options, palliative measures have been the core of the treatment approach for most NSCLC patients (Schiller, 2002). However, with improvement in the area of scientific discoveries and clinical findings, treatment options have expanded to include many targeted molecular therapies such as epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).

The first EGFR-TKI studied in NSCLC patients was gefitinib (Iressa) (Fukuoka et al., 2003). Phase II trials with EGFR-TKIs showed positive results in response rate (Fukuoka et al., 2003; Kim et al., 2008). Subsequently, this led to large phase III trials, including the first-line Iressa vs. Carboplatin/Paclitaxel in Asia (IPASS) study published in 2009 and the Japanese study based on the analysis of EGFR mutation status (North-East Japan Study Group) discussed here (Maemondo et al., 2010). Kris et al. (2003) have previously reported that the sensitive clinical factors for effectiveness in EGFR-TKIs are Asian ethnicity, female gender, never-smokers, and adenocarcinoma histology. Although the IPASS trial was designed and conducted using the clinical factor of nonsmoking/light smoking status as the primary method of analysis (Mok et al., 2009), the North-East Japan Study Group trial was primarily based on the molecular factor of EGFR mutation status with the primary endpoint of progression-free survival and secondary endpoints of overall survival (OS), response rate (RR), and toxic effects.

Study Design, Efficacy, and Safety

In this phase III, multicenter, randomized trial, 230 eligible patients (chemonaive, age ≤ 75, advanced NSCLC harboring sensitive EGFR mutations, and the absence of the resistant

EGFR mutation T790M) were stratified according to sex, clinical disease stage, and institution. Patients were randomly assigned to receive either gefitinib or standard chemotherapy (paclitaxel plus carboplatin). Gefitinib was given until disease progression, intolerable toxic effects, or withdrawal of consent. Chemotherapy was given for a minimum of three cycles.

The results indicated that the patients with advanced NSCLC who harbored sensitive EGFR mutations had improved progression-free survival compared to standard chemotherapy with a hazard ratio (HR) of 0.36 and a p value of < .001. Additionally, the gefitinib group had a significantly longer median progression-free survival (10.8 vs. 5.4 months) compared to the chemotherapy group (HR 0.30; p < .001). However, the median OS was not significant (p = .31). Maemondo et al. (2010) reached the same conclusion as had been reported in the prior phase III IPASS trial: that the presence of the EGFR gene mutation in the tumor was a strong predictor for a better outcome with gefitinib as compared with standard chemotherapy.

The most common side effects in the gefitinib group were rash and elevated aspartate aminotransferase or alanine aminotransferase. The chemotherapy group most commonly experienced appetite loss, neutropenia, anemia, and sensory neuropathy. In the gefitinib group, six patients experienced interstitial lung disease (three severe, one of these fatal) and one experienced a grade 4 seizure. Once grade 4 cerebral infarction and one grade 4 bowel obstruction were seen in the chemotherapy group. Overall, the incidence of severe toxic effects (National Cancer Institute Common Toxicity Criteria grade ≥ 3) was significantly higher in the chemotherapy group (71.7%) vs. the gefitinib group (41.2%; p < .001).

Clinical Implications

So what does this mean and where does this lead us with respect to current lung cancer treatment options and the incorporation of EGFR-TKI therapies? In their conclusion, Maemondo et al. state, "Selection of patients on the basis of EGFR mutation status is strongly recommended." As with other targeted therapies, this is significant because it adds more information toward getting that crucial first-line treatment choice correct. It is a step forward in the chapter of lung cancer treatment development in the new era of personalized targeted therapies. In many clinical settings, it would be recommended that patients diagnosed with advanced-stage NSCLC (especially with nonsquamous histology) be tested for EGFR mutation status to determine their eligibility for receiving an EGFR-TKI agent as the first line of therapy. Currently, an increasingly large number of oncologists have been ordering EGFR mutation biomarker testing on patients' tissue specimens whenever possible. EGFR biomarker testing is routinely performed at most of the large academic institutions. Unfortunately, many lung cancer pathology specimens do not contain an adequate amount of tumor for testing. In many cases, oncologists are recommending fresh core biopsies from patients in order to perform the biomarker test prior to initiating treatment.

About Gefitinib Administration

Standard treatment with gefitinib is 250 mg orally once a day on an empty stomach, with patients continuing the drug until disease progression or until unacceptable toxicities occur. Patients should have follow-up visits at regular intervals to assess side effects or toxicities, as well as updated CT and/or PET scans and blood tests, including liver function tests.

Conclusion

Non–small cell lung cancer patients now have an alternative treatment option compared to traditional chemotherapy, with a generally more benign side-effect profile. As we continue to explore and improve upon treatment options for lung cancer patients, clinicians have become increasingly excited by the possibility of offering a treatment that offers considerable benefit to selected patients.

DISCLOSURES

The author has no potential conflicts of interest to disclose.

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