Perspective

Front-line erlotinib in unselected patient with advanced NSCLC followed by standard chemotherapy with gemcitabine and cisplatin - TORCH study

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Result from BR. 21 study demonstrated that in unselected patients with advanced non-small cell lung cancer (NSCLC) pretreated with standard first-line or second-line chemotherapy, subsequent erlotinib treatment prolonged overall survival (OS) as compared to placebo (1). Erlotinib was evaluated as front-line therapy for unselected patients with advanced NSCLC. In a phase II study of erlotinib in NSCLC patients, Giaccone *et al*. (2) demonstrated a tumor response rate of 22.7% and a median overall survival of 391 days. In elderly patients treated with front-line erlotinib, the response rate was 10%, and median time-to-progression (TTP) and overall survival (OS) were 3.5 and 10.9 months respectively (3).

Based on these studies, a phase III TORCH (Tarceva or Chemotherapy) study was conducted to evaluate the value of front-line erlotinib in unselected NSCLC patients. Stage IIIB/IV NSCLC patients were randomized to receive erlotinib followed by gemcitabine and cisplatin at the time of progression, or the reverse order of gemcitabine and cisplatin followed by erlotinib at the time of progression. The primary endpoint was OS. The study was designed to show non-inferiority of erlotinib used as front-line compared to standard use of chemotherapy as front-line. Unlike other phase III studies of front-line single agent EGFR TKI therapy, which selected patients according to the clinical characteristics (4,5) or predictive biomarkers (6-9) (e.g., *EGFR* mutation status), this study enrolled the whole population with advanced NSCLC in a predominant Caucasian population. In addition, this study was the only study that restricted the second-line therapy after first disease progression.

The study was conducted in Italy and Canada between December 2006 and November 2009. A total of 900 patients (and 669 events were needed) was planned based on a hazard ratio (HR) of 95% confidence interval lower limit of 1.25. The study was early-terminated at first interim analysis due to futility test. In a recent issue of *Journal of Clinical Oncology*, Gridelli *et al*. (10) reported the final result of TORCH study. Seven hundred sixty patients (380 patients in both arms) were randomly assigned to two arms stratified by histology, smoking status, sex, age, study center, and performance status. Around one-third (33.7%) of the patients were females, most of the study patients (79.3%) were former or current smokers, 44.5% of the patients had histology other than adenocarcinoma or bronchioalveolar carcinoma, and only 3.2% have East Asian ethnicity. After front-line treatment, 41.7% of the 333 patients with documented progressive disease (PD) in the experimental arm did not received pre-planned second-line chemotherapy with gemcitabine plus cisplatin regimen. In the standard treatment arm, 28.5% of the 316 patients with documented PD did not receive subsequent erlotinib treatment. These patients did not receive subsequent treatment because of worsening condition or death. *EGFR* mutation status (exon 19 and exon 21) was available in 275 patients (36.2%). Among these patients, 39 patients (14.2%) had *EGFR* mutation-positive tumors (19 in the experimental arm). Efficacy analysis was conducted on an intent-to-

treat basis. With a median follow-up of 24.3 months, the median survival was 11.6 months (95% CI, 10.2 to 13.3 months) in the standard arm and 8.7 months (95% CI, 7.4 to 10.5 months) in the experimental arm. Adjusted HR of death in the experimental arm was 1.24 (95% CI, 1.04 to 1.47). There was no heterogeneity of treatment effect among subgroups including sex, histology, smoking status and *EGFR* mutation status.

Progression-free survival (PFS) was the secondary endpoint. The median PFS was 2.2 months in the experimental arm and 5.4 months in the standard treatment arm (HR=1.53, 95% CI, 1.31 to 1.77). There was significant interaction with sex (P=0.014), smoking status (P<0.001), and *EGFR* mutation status (P=0.006).

Total progression free survival (total PFS) was also designed as secondary endpoint and was defined as the time from random assignment to progression after second-line treatment or death if it occurred before second progression or last follow-up for patients who were not included in the aforementioned categories. Total PFS was 6.4 and 8.9 months in the experimental arm and standard treatment arm respectively; adjusted HR for progression was 1.21 (95% CI, 1.04 to 1,42). There was no heterogeneity of treatment effect among subgroups including sex, histology, smoking status and *EGFR* mutation status.

The objective response rate of front-line erlotinib treatment was 8.7% as compared to 25.6% in the standard chemotherapy arm. Among those patients who underwent pre-planned second-line therapy, the objective response rate was 20.6% (second-line gemcitabine plus cisplatin chemotherapy) in the experimental arm as compared to 8% (second-line erlotinib) in the standard treatment arm. The difference between the two arms was significant (P<0.001). In those patients with *EGFR* mutation-positive tumors, the response rate of front-line erlotinib was 42.1% and 25% for front-line standard chemotherapy.

This is the first and probably the last and only phase III randomized study to evaluate the efficacy of front-line erlotinib versus chemotherapy in unselected Caucasian patients with advanced NSCLC. EURTAC study was conducted in France, Italy and Spain, and patients were selected by *EGFR* mutation status (exon 19 deletion or L858R) (9). A total of 173 patients were randomly assigned to receive either erlotinib (n=86) or cisplatin plus gemcitabine or docetaxel. More than 90% of patients had adenocarcinoma histology. 69% of the patients were never-smokers, 72.8% of the patients were female. These basic characteristics were different from those in TORCH study. The primary endpoint of EURTAC study was PFS. PFS was superior for erlotinib compared to the platinum-based chemotherapy (median PFS 9.7 *vs*. 5.2 months; HR=0.37; 95% CI, 0.25 to 0.54; P<0.0001). The tumor response rates in the erlotinib arm and chemotherapy arm were 58% and 15% respectively, similar to the response rates of *EGFR* mutation-positive patients in TORCH study (42% versus 25%). Several randomized studies demonstrated superior PFS for *EGFR* mutation-positive patients treated with gefitinib or erlotinib versus chemotherapy. *EGFR* mutation test is recommended to select patients suitable for front-line *EGFR* TKI monotherapy (11). However, in all these studies, there were no OS advantages for patients to start treatment with gefitinib or erlotinib. The lack of OS difference for patients treated with front-line gefitinib or erlotinib versus chemotherapy may be due to the extensive crossing over of subsequent second-line treatment as well as uncontrolled second-line treatment options. In TORCH study, the second-line treatment was pre-planned and controlled. However, more patients in the standard treatment arm received second-line erlotinib (226/316) than patients in the experimental arm who received subsequent chemotherapy (194/333). In the experimental arm, patients who experienced disease progression after erlotinib therapy may be too weak to undergo second-line cytotoxic chemotherapy. Given the ineffectiveness of erlotinib in unselected patients, the difference of OS reflected the different proportion of patients who were capable to undergo cytotoxic chemotherapy.

EGFR mutation (exon 19 and exon 21) status was available in 36.2% of all the TORCH study population and 14.2% of them harbor *EGFR* mutation. The PFS was 6.9 months for front-line chemotherapy and 9.7 months for erlotinib, similar to EURTAC study results. However, when the total PFS was compared, patients who started with chemotherapy seemed to do better than patients started with erlotinib. The superiority of OS in patients treated with front-line chemotherapy was also consistent with the total PFS trend. However, the number of patients with *EGFR* mutation in TORCH was too small (N=39) for any conclusion.

Can we conclude from this study and the recent TAILOR study that erlotinib was not effective in *EGFR* wild-type patients (12)? We can only conclude from these two studies that erlotinib was not as good as chemotherapy when chemotherapy is a recommended treatment as front-line and second-line setting. When erlotinib was compared to placebo, such as BR. 21 or SATURN study,

a survival advantage was clearly shown (1,13). These trial results suggest that erlotinib may be useful for *EGFR* wild-type NSCLC patients when chemotherapy is not an option. However, the low response rates and small survival difference suggest that only small fraction of patients had benefit or most patients had only small benefit. Further studies can be focused on identifying these patients or augment the benefit of erlotinib in *EGFR* wild-type patients when we exhaust traditional wisdom of chemotherapy.

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