Review

Intercalated Chemotherapy and Epidermal Growth Factor Receptor Inhibitors for Patients With Advanced Non–Small-cell Lung Cancer: A Systematic Review and Meta-analysis

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Abstract

Randomized clinical trials (RCTs) of concurrent epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) plus chemotherapy for unselected patients with advanced non–small-cell lung cancer (NSCLC) produced negative results. Intercalated administration could avoid the reduction of chemotherapy activity due to G_1 cell-cycle arrest from EGFR-TKIs. A PubMed search was performed in December 2015 and updated in February 2016. The references from the selected studies were also checked to identify additional eligible trials. Furthermore, the proceedings of the main international meetings were searched from 2010 onward. We included RCTs comparing chemotherapy intercalated with an EGFR-TKI versus chemotherapy alone for patients with advanced NSCLC. Ten RCTs were eligible (6 with erlotinib, 4 with gefitinib): 39% of patients had a known *EGFR* mutational status, 43% of whom *EGFR* mutation positive. The intercalated combination was associated with a significant improvement in overall survival (OS; hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.71-0.95; $P = .01$), progression-free survival (PFS; HR, 0.60; 95% CI, 0.53-0.68; $P < .00001$), and objective response rate (ORR; odds ratio [OR], 2.70; 95% CI, 2.08-3.49; $P < .00001$). Considering only first-line trials, similar differences were found in OS (HR, 0.85; 95% CI, 0.72-1.00; $P = .05$), PFS (HR, 0.63; 95% CI, 0.55-0.73; $P < .00001$), and ORR (OR, 2.21; 95% CI, 1.65-2.95; $P < .00001$). In *EGFR* mutation-positive patients, the addition of an intercalated EGFR-TKI produced a significant benefit in PFS (129 patients; HR, 0.24; 95% CI, 0.16-0.37; $P < .00001$) and ORR (168 patients; OR, 11.59; 95% CI, 5.54-24.25; $P < .00001$). In patients with advanced NSCLC, chemotherapy plus intercalated EGFR-TKIs was superior to chemotherapy alone, although a definitive interpretation was jeopardized by the variable proportion of patients with *EGFR* mutation-positive tumors included.

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Introduction

Non–small-cell lung cancer (NSCLC) represents about 85% of all new lung cancer cases diagnosed worldwide every year.[1] Considering that most cases of NSCLC are diagnosed with an advanced stage of disease already present, systemic palliative therapy is the mainstay of treatment. The discovery of oncogene-addicted NSCLC, mainly due to the presence of epidermal growth factor receptor (*EGFR*)-activating mutations or anaplastic lymphoma kinase (*ALK*) and proto-oncogene tyrosine-protein kinase reactive oxygen species (*ROS1*) translocations, is of paramount importance to select patients who could benefit much by the use of the corresponding inhibitors. However, in this era of personalized medicine, only about 20% of white patients present such genetic alterations; thus, in most cases, platinum doublets represent the standard of care for first-line therapy.[2,3]

Early trials investigated EGFR-tyrosine kinase inhibitors (TKIs) in combination with platinum-based chemotherapy as continuous administration, showing no improvements in any outcome

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compared with chemotherapy alone.[4-7] In contrast, single-agent EGFR-TKIs are the standard of care for the treatment of patients affected by advanced NSCLC harboring activating *EGFR* mutations, because these drugs proved to be superior to platinum-based chemotherapy in terms of both efficacy and tolerability.[8-14]

A possible explanation of the negative results obtained with the combination of chemotherapy with continuous administration of an EGFR-TKI is that the G_1 cell-cycle arrest caused by EGFR-TKIs might reduce the cell-cycle phase-dependent activity of the chemotherapy.[15-18] In contrast, preclinical data showed that sequential, intercalated administration of TKIs after chemotherapy might be effective.[19,20] In the clinical setting, the intercalated regimen consists of the sequential administration of chemotherapy and an EGFR-TKI on different days of each cycle of therapy.

With these considerations, single-arm phase II studies investigated the activity of an intercalated schedule of erlotinib or gefitinib plus chemotherapy for patients with advanced NSCLC. Some of these trials studied the regimen as first-line treatment,[21-26] and others were conducted in pretreated patients.[27-29] Overall, the results of these studies indicated that the intercalated strategic approach for EGFR-TKI and chemotherapy could represent a potential treatment option for patients with advanced NSCLC. These studies were used as the proof-of-concept for several comparative trials.

Our objective was to perform a systematic review and meta-analysis of randomized clinical trials (RCTs) comparing the combination of chemotherapy plus intercalated EGFR-TKIs versus chemotherapy alone in patients with advanced NSCLC in terms of overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and toxicity.

Patients and Methods

Data Sources

The full protocol of the review is available on request from one of us (A.R.). A PubMed search was performed in December 2015 and updated in February 2016 to identify all trials that had investigated chemotherapy intercalated with an EGFR-TKI for patients with advanced NSCLC. The following keywords were used: ("gefitinib" OR "erlotinib" OR "afatinib") AND "NSCLC." The references of the selected reports were also reviewed to identify additional eligible trials. Furthermore, the proceedings of the main international meetings (American Society of Clinical Oncology and European Society of Medical Oncology annual meetings) were searched from 2010 onward for relevant abstracts. When >1 report was available describing the same trial, the most recent information (corresponding to a longer follow-up period and greater number of events) was included in the analysis. For each study, the quality of the randomization process was evaluated using the information available in the report.

Study Selection, Data Extraction, and Data Synthesis

Of the trials identified in the present systematic review, all RCTs comparing the intercalated administration of EGFR-TKI plus chemotherapy versus the same chemotherapy alone were included in the meta-analysis.

The data were extracted independently by 2 of us. After the data were abstracted from each study, a meta-analysis was performed using RevMan, version 5.3, software. The primary endpoint of the meta-analysis was OS. The secondary endpoints were PFS, ORR, and toxicity.

For OS and PFS, the efficacy data from all randomly assigned patients were analyzed on an intention-to-treat basis. For ORR, some randomized patients were excluded from the activity analysis according to the information reported for each trial. For both OS and PFS, the summary measure was the hazard ratio (HR), with the 95% confidence interval (CI). For the ORR, the summary measure was the odds ratio (OR), with the 95% CI. A fixed-effects model was applied. Statistical heterogeneity between studies was examined using the χ^2 test and I^2 statistic. Subgroup analyses were conducted considering only the first-line trials and including patients with *EGFR* mutation-positive tumors alone, if the latter subgroup had been separately described in the trial.

The following toxicities were considered, if available in the reports: skin rash, diarrhea, nausea, vomiting, anemia, neutropenia, thrombocytopenia, fatigue, and liver toxicity. In each trial, only patients who had received ≥ 1 treatment dose were included in the toxicity analysis. For each toxicity, the treatment groups were compared in terms of the proportion of any grade of toxicity and in terms of severe toxicity (grade ≥ 3). The summary measure for all the toxicities was the OR and 95% CI.

Results

Our PubMed search identified 4732 studies. After the exclusion of 4711 references by reading the title or the abstract, we identified 21 potentially eligible reports (Supplemental Figure 1; online version). Another 4 trials were identified from the proceedings of American Society of Clinical Oncology and European Society of Medical Oncology meetings. Of these 25 trials testing an intercalated schedule of EGFR-TKI plus chemotherapy for patients affected by advanced NSCLC, 15 were not designed to compare the combination with the use of chemotherapy alone.[21-35] Some of these trials were noncomparative,[21-29] and others compared the intercalated combination of EGFR-TKI plus chemotherapy versus EGFR-TKI alone.[30-35] However, the latter comparison was of limited relevance for patients unselected for *EGFR* mutational status, because EGFR-TKI alone has limited activity and represents a weak control arm. With this type of comparison, it is difficult to determine whether the result in the experimental arm was associated with the intercalated combination or whether it could have been obtained with chemotherapy alone.

Finally, we identified trials comparing the intercalated combination of EGFR-TKI plus chemotherapy versus chemotherapy alone.[36-45] This issue has potential clinical relevance, and trials with this design were eligible for our meta-analysis. Overall, 10 RCTs, with a total of 1408 patients, compared the intercalated combination of EGFR-TKI plus chemotherapy versus chemotherapy alone. The main characteristics of these 10 RCTs are reported in Table 1. In detail, 6 RCTs tested the addition of erlotinib to chemotherapy[36-41] and 4 tested the addition of gefitinib.[42-45] None of the eligible trials had studied afatinib.

Of these 10 studies, 8 were phase II RCTs[36,37,39-44] and 2 were phase III RCTs.[38,45] The primary endpoint was PFS in 6 trials,[37-41,45] the progression-free rate at specific measurement points in 3 trials (after 8 weeks,[36] after 12 weeks,[42] and after 6 months[43]), and the ORR in 1 trial.[44] The 10 RCTs were heterogeneous in terms of the