Maintenance or Consolidation Therapy for Non–Small-Cell Lung Cancer: A Meta-Analysis Involving 5841 Subjects

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Abstract

The reports of recent clinical trials have described safety and efficacy of maintenance therapy in non–small-cell lung cancer (NSCLC), but there are still controversies in conclusions. In this meta-analysis, we summarize 14 major clinical trials of maintenance therapy in NSCLC, and the outcome showed that some of them for advanced NSCLC patients after first-line treatment can improve overall and/or progression-free survival.

Introduction: Maintenance therapy is a new treatment paradigm for advanced non–small-cell lung cancer (NSCLC). We conducted a meta-analysis to evaluate its clinical efficacy in NSCLC and compared the efficacy of chemotherapy, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), and other treatment approaches. **Materials and Methods:** Electronic databases were obtained from published reports of randomized controlled trials (RCTs) that compared maintenance or consolidation therapy with placebo, best supportive care (BSC) or just observation. Hazard ratios for progression-free survival (PFS) and overall survival (OS), with their relative 95% confidence intervals (CIs), were derived. All statistical analyses were conducted with RevMan 5.0 software, and statistical significance was defined as $P < .05$. **Results:** A total of 14 RCTs involving 5841 patients were eligible for our analysis, including chemotherapy used in 5 RCTs, EGFR-TKI in 6, and others (eg, biotherapy) in 3. Our study showed that compared with the control, maintenance or consolidation therapy could prolong the OS (odds ratio [OR], 0.84; 95% CI, 0.75-0.95; $P = .005$) and PFS (OR, 0.63; 95% CI, 0.54-0.73; $P < .00001$) periods. Subgroup analysis showed that chemotherapy can improve PFS but not OS, EGFR-TKI can improve PFS and OS, and other therapies can improve neither PFS nor OS. **Conclusion:** Our meta-analysis demonstrated that maintenance therapy for advanced NSCLC patients can decrease the PFS risk to 0.63 and OS to 0.84. However, its clinical effect has yet to be confirmed by further studies.

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Introduction

Lung cancer remains the most common malignancy and the leading cause of cancer-related mortality worldwide; approximately 80% of cancers are classified as non–small-cell lung cancer (NSCLC).[1] Approximately 85% to 90% of the disease is defined as being at the advanced or metastatic stage (IIIB or IV)[2] and unsuitable for surgery. Chemotherapy with platinum-based regimens has been beneficial in symptom control and in prolonging life expectancy in advanced-stage patients. However, these benefits are modest. Most patients experience disease progression and finally succumb to advanced NSCLC after first-line chemotherapy. Platinum-based chemotherapy is generally restricted to 4 to 6 cycles in the first-line setting. Extended chemotherapy with combination regimens in more than 4 to 6 cycles results only in additional toxicity without meaningful improvement in response, progression-free survival (PFS), and overall survival (OS).[3] One of the strategies currently used to prolong survival in NSCLC patients is maintenance treatment after first-line chemotherapy.

Maintenance therapy, also known as "early second-line" chemotherapy or consolidation therapy,[4,5] has been defined as the treatment administered after the end of first-line chemotherapy cycles in patients whose disease has been controlled. Maintenance therapy typically continues until the occurrence of intolerable toxicity or disease progression. Drugs used in maintenance therapy for NSCLC could be either one of the drugs in the induction

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chemotherapy protocol or another drug with less toxicity and no cross-resistance. Maintenance therapy was proposed by Goldie et al in 1982 because of the feasibility of increasing the power of killing malignant cells before drug resistance using non–cross-suppressing drugs and by optimizing the therapeutic effect.[6] However, controversies arise as to whether maintenance therapy might improve the efficacy. To evaluate the significance of maintenance therapy, we performed a meta-analysis on randomized controlled trials (RCTs) with reference to maintenance or consolidation therapy for unresectable stage III/IV NSCLC. This meta-analysis was performed on 14 RCTs (and included 5841 subjects) in which maintenance or consolidation therapy was compared against placebo in the maintenance regimen for patients with advanced NSCLC to quantify potential benefits and determine safety. Our outcome showed that chemotherapy maintenance treatment can improve PFS but not OS; epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) can prolong PFS and OS; but other treatments do not get a positive result.

Materials and Methods

Search Strategy

A comprehensive literature search through the PubMed database (from August 31, 2003 to August 31, 2013) of the US National Library of Medicine was conducted using search terms including "NSCLC," "non–small-cell lung cancer," "maintenance therapy," "consolidation therapy," "randomized controlled trial," and "RCT." The Boolean operator between "NSCLC" and "non–small-cell lung cancer," "maintenance therapy" and "consolidation therapy," and "randomized controlled trial" and "RCT," was "or." The Boolean operator between other terms was "and." To identify additional studies, we also conducted a manual search of references cited in original studies or reviewed articles on this topic. The following criteria were used to select the eligible studies: (1) the type of study should be RCT; (2) randomization should be performed after any induction chemotherapy, and the study should have sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI); (3) the patients must be diagnosed pathologically or cytologically and at clinical stage III to IV, achieve a nonprogressive disease at the end of a defined number of induction chemotherapy cycles; and (4) the patients in the experimental group should be given different drugs as maintenance therapy, and the patients in the control group should be given placebo without any anticancer treatments; the same best supportive care (BSC) in both groups was performed. Studies were excluded based on the following criteria: (1) the type of study was not RCT; (2) the studies were reviews of this topic; (3) data could not be extracted completely; and (4) as Little et al[7] recommended, when several publications reported on the same population data, only the most recent or largest was selected.

Outcome Definition

Two investigators independently extracted the data. For each eligible study, the following information was recorded: name of first author, year of publication, proposal of induction therapy and maintenance therapy, number of cases in different groups, OS and PFS of patients in different groups, and main related adverse effects.

Maintenance therapy was considered an experimental arm of the study, and placebo or control was considered a comparator. The primary outcome was OS, which was defined as the time between randomization and death for any cause or date of last follow-up visit for survival cases. The secondary outcome was PFS, which was defined as the time between randomization and progression of disease, death without progression, or date of last follow-up visit for patients alive without progression. We considered the toxicity of maintenance therapy as another end point.

Figure 1 Flow Chart of Study Selection