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Review

Single-agent versus combination chemotherapy as first-line treatment for patients with advanced non-small cell lung cancer and performance status 2: A literature-based meta-analysis of randomized studies

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ABSTRACT

Background: The purpose of this study was to compare the efficacy and tolerability of first-line treatment with combination versus single agent chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) 2.
Methods: A systematic literature search was performed to identify randomized trials comparing combination versus single agent chemotherapy in patients with advanced NCSLC. Both trials dedicated to PS 2 patients and trials that performed a subset analysis according to PS were included in the meta-analysis. Standard meta-analytic procedures were used to analyze the study outcomes.
Results: Twelve trials were considered eligible and were further analyzed. The use of combination chemotherapy resulted in a statistically significant better overall survival compared to single agent chemotherapy (11 trials, 1114 patients; hazard ratio (HR), 0.79, 95% confidence interval (CI): 0.71–0.88). The survival benefit was pronounced when platinum-based combination was used (HR: 0.71, 95% CI: 0.61–0.81) while no survival benefit was observed in non-platinum based combinations (HR: 0.96, 95% CI: 0.80–1.15). Grade 3/4 anemia (OR: 3.12, 95% CI: 1.55–6.27), thrombocytopenia (OR: 12.81, 95% CI: 4.65–33.10), and neutropenia (OR: 7.91, 95% CI: 3.97–15.78) but not febrile neutropenia were significantly more frequent with combination chemotherapy.
Conclusion: This meta-analysis provides evidence supporting the use of combination chemotherapy in patients with NSCLC and PS 2. However, the patients should be informed about the higher risk for toxicity with the combination chemotherapy and the final treatment strategy should be individualized.

1. Introduction

Lung cancer is the leading cause of cancer death worldwide and non-small-cell lung cancer (NSCLC) accounts for approximately 80% of lung cancer cases [1]. Because the majority of patients present with metastatic disease palliative treatment is often the only therapeutic option. Treatment with platinum-based combination chemotherapy is considered standard of care for patients with metastatic NSCLC and performance status (PS) 0–1 since it has been shown to be superior to single agent treatment and marginally superior to non-platinum combinations in terms of overall survival [2,3].

A substantial number of patients with metastatic NSCLC present with a PS 2 [4]. These patients have significantly impaired survival compared with PS 0–1 patients [5,6]. Because of concerns about excess toxicity with combination therapy in patients with PS 2, single-agent therapy has become an accepted treatment standard [2,3,7]. Regarding the use of combination chemotherapy in these patients, the National Comprehensive Cancer Network and a panel of European experts have concluded that carboplatin-based doublets are a reasonable alternative in selected cases [2,7], while the American Society of Clinical Oncology guidelines recognize that the data are insufficient to make any recommendation because the available evidence is mainly coming from subgroup analysis within phase III trials [3]. However, these subgroup analyses of randomized trials are prone to selection bias as patients with PS 2 are a very heterogeneous category of patients.

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Recently, several randomized trials specifically focusing on PS 2 patients with advanced NSCLC have been published and their results are able to improve the quality of evidence [8–11].

The purpose of our meta-analysis was to investigate the efficacy and tolerability of combination chemotherapy in comparison with single agent treatment in patients with metastatic NCSLC and PS 2.

2. Patients and methods

2.1. Search strategy

We conducted a computer-based search of Medline, and the Cochrane Library without year and language restrictions, by using algorithms including the following keywords: chemotherapy, performance status, non-small cell lung cancer, NSCLC. The last search was updated in July 2013.

To locate unpublished trials, we searched the electronic abstract databases of the American Society of Clinical Oncology Annual Meeting. We also conducted secondary referencing by manually reviewing reference lists of potentially eligible articles. Additional studies were identified by screening reference lists of identified studies and reviews.

When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial.

2.2. Study selection

We included all randomized trials that evaluated the administration of combination versus single-agent chemotherapy in untreated patients with advanced NSCLC and PS 2, according to the Eastern Cooperative Oncology Group scale. We included both trials dedicated to PS2 patients and trials that performed a subset analysis according to PS as long as they had a randomized design.

We excluded non-randomized trials, trials in which combination chemotherapy was given in both treatment arms and trials that included patients with PS 3 or pretreated patients.

2.3. Data extraction

Data extraction was conducted independently by two investigators (CM and AV) according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [12], and any discrepancies among reviewers were resolved by consensus.

For each study, we extracted the following information: authors' names, journal and year of publication, country of origin, years of patient enrollment, and number of centers involved; number of patients randomized and analyzed per arm, dose of regimens, sex, age, type of histology (squamous cell carcinoma, adenocarcinoma), stage of disease (stage IIIB, IV), data on outcome measures.

In case of insufficient information in the original publication, we contacted authors of the primary studies for additional data.

2.4. Risk of bias and publication bias assessment

Cochrane's risk of bias tool has been utilized in order to assess the individual risk of bias of each study. The criteria used for quality assessment were sequence generation of allocation, allocation concealment, masking of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. Two authors (CM, AV) independently assessed the risk of bias in each eligible trial.

Publication bias was assessed with the construction of contour enhanced funnel plots.

2.5. Outcome measures

The primary outcome of the meta-analysis was the overall survival (OS) in patients treated with combination versus single-agent chemotherapy.

Secondary outcomes were progression-free survival (PFS), objective response rate (ORR) defined as the number of complete and partial response in each treatment arm, grades III and IV toxicity rates and death due to toxicity.

2.6. Data synthesis and analysis

The combination chemotherapy was considered an investigational treatment, and the single agent was used as a control treatment.

The number of objective responses and toxicities were retrieved from each primary study and 2×2 tables were constructed. We calculated an overall effect estimate for all dichotomous data as an odds ratio (OR) with 95% confidence interval (CI). We assessed the presence of statistical heterogeneity among the studies by using the Q statistics and the magnitude of heterogeneity by using the I^2 statistic. We considered a p-value < 0.10 or an I^2 value of greater than 50% as indicative of substantial heterogeneity. When substantial heterogeneity was not observed, the pooled OR calculated based on the fixed-effects model using the Mantel Haenszel method. When substantial heterogeneity was observed, the pooled OR was calculated based on the random-effects model was reported using the DerSimonian and Laird method.

For the time-to-event outcomes (PFS, OS), we performed a meta-analysis first by transforming the Hazard Ratio (HR) and their errors into their log counterparts, and then using the inverse variance method and then transformed back into the HR scale. If time-to-event data were unavailable for direct extraction from the original publication, we extracted data according to the method described by Tierney et al. [13]. This method allows calculation of the hazard-ratio from different parameters using indirect calculation of the variance and the number of observed minus expected events.

We performed the following subgroup analyses in the meta-analysis: according to type of study regarding PS analysis (trials dedicated to PS2 patients, trials with subset analysis based on PS), and type of combination chemotherapy used (platinum-based chemotherapy, non-platinum based chemotherapy).

All reported p values are 2-sided, with significance set at $p < 0.05$. All statistical analyses were performed with RevMan 5.0.

3. Results

3.1. Study selection

Our initial search yielded a total of 830 potentially relevant trials. Of these, 804 were excluded on the basis of the abstract or title leading to 26 potentially eligible trials. A flow chart indicating the identification of randomized controlled trials for inclusion in the meta-analysis is shown in Fig. 1.

3.2. Trials characteristics

Characteristics of each study are presented in Table 1. The 12 eligible trials included 1268 patients. Four trials [8–11] were dedicated to PS 2 patients while eight [14–21] were randomized trials that performed a subset analysis according to PS. The chemotherapies used in combination arms were platinum-based in nine trials [8–11,15,17,18,20,21] and non-platinum based in three [14,16,19].

Three trials [14,17,19] were multiple-armed and some assumptions were made before inclusion in the meta-analysis. Le Chevalier et al. [17] conducted a three-arm randomized trial comparing