Interpreting Clinical Trials in Lung Cancer: Impact of Methodology and Endpoints

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Abstract: The design and analysis of clinical trials are crucial if we are confidently to answer important questions regarding the treatment of patients with non-small cell lung cancer. Survival, response, and quality of life (QoL) are considered the key endpoints of oncology clinical trials. Survival is the primary endpoint of most randomized, phase III clinical trials, but small improvements in survival are difficult to detect without a sufficiently large sample size. Meta-analysis is a useful technique to increase statistical precision and better estimate the magnitude of a treatment effect. Although survival data guide treatment choice, the objective response is generally the parameter used to evaluate treatment in the clinic, despite its inherent unreliability. The objective response rate remains an important outcome for early phase clinical trials. QoL, which is a particularly important trial endpoint if survival differences are unlikely may, however, be a more relevant outcome in the clinic. Several validated QoL tools are available for use both in trials and in daily practice, but many clinicians do not routinely assess QoL when evaluating an individual patient's response to treatment. Recent advances in electronic technology make capturing QoL data at each office visit not only possible but practical, reliable, and useful for both patients and clinicians. Therefore, although survival, response, and QoL can all be relevant clinical trial endpoints, QoL may be the most relevant endpoint to assess in the clinic.

Key Words: Non-small cell lung cancer, Endpoints, Quality of life, Response, Survival, Docetaxel.

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INTRODUCTION

Providing the best treatment for patients with lung cancer requires a clear interpretation of the results of clinical trials. Trials differ, however, in the population studied, the analytical methods used, and the treatments evaluated. Health services research groups in oncology have identified survival, response, and quality of life (QoL) as the key endpoints in clinical trials. In large randomized trials, response is generally not considered to be sufficiently reliable to be a primary endpoint, but may be useful in small studies estimating some degree of anticancer activity. Other endpoints, such as disease-free survival, duration of response, and symptom control, are related to these key areas, but are seen as secondary endpoints in patients with lung cancer. The role of each of these endpoints differs between clinical trial interpretation and clinical decision-making for individual patients. Survival results are clearly important when recommending a particular treatment, but are not helpful once the patient is receiving therapy. Response is generally the endpoint used in clinical decision-making, but it is the least reliable, most expensive, and most intrusive endpoint to assess. It may be of little value to patients unless accompanied by an improvement in survival, QoL, or both. QoL is an increasingly reliable endpoint that is feasible to evaluate in the clinic. This review examines the strengths, weaknesses, and appropriate use of each of the key endpoints.

SURVIVAL

Overall survival is widely accepted as the most appropriate endpoint for randomized clinical trials. It is reliable, realistic, objective, and easily determined. A treatment that produces a significant survival benefit in a well-designed randomized trial is likely to garner regulatory approval in the United States and Europe. The US Food and Drug Administration and the European Medicines Agency consider overall survival the most appropriate endpoint for non-small cell lung cancer (NSCLC) clinical trials. When considering survival, however, we must distinguish larger treatment goals from reasonable trial endpoints. For example, increasing median survival from 8 to 12 months may be a laudable long-term goal in advanced NSCLC, but it is not an appropriate endpoint for a clinical trial. Realistic differences between treatment arms are likely to be small, and to detect small differences, a relatively large sample size is required. Statistical power can be increased by pooling the results of randomized clinical trials with meta-analytical techniques. Meta-analysis can also be used to increase the precision of the treatment effect and to reconcile seemingly discordant clinical trial results. In NSCLC, meta-analyses have confirmed the benefit of chemotherapy over best supportive care, supported the use of chemotherapy in the adjuvant setting, established the superiority of doublets over monotherapy but the lack of additional benefit with three-drug regimens, and indicated response and survival advantages with cisplatin compared with carboplatin or other non-platinum-based regimens (Table 1).[1–7]

Despite the improvements in survival associated with cisplatin-based therapy, many clinicians have remained

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TABLE 1. Results of Meta-Analyses in Non-small Cell Lung Cancer.

Study	Studies Included	Combined *N*	Comparison	Outcome
Advanced disease				
NSCLC Collaborative Group[1] (1995)	8 RCT	778	Combination, cisplatin-based chemo vs BSC	27% reduction in risk of death when chemotherapy added to BSC (HR 0.73, $p < 0.0001$) Equivalent to increase in MST of 1.5 months
Delbaldo et al.[2]	65 RCT	13 601	(1) Doublet vs single-agent therapy	20% reduction in odds of death at 1 year with doublet therapy (OR 0.80, $p < 0.001$)
			(2) Triplet vs doublet therapy	No difference (OR 1.01) for triplet vs doublet
Hotta et al.[3]	8 RCT	2948	Cisplatin-based vs carboplatin-based chemo	No survival advantage with cisplatin overall (HR 1.05, $p = 0.5$) Cisplatin plus new agent improved MST relative to carboplatin plus new agent (HR 1.106, $p = 0.039$)
Barlesi et al.[4]	14 RCT	5943	Cisplatin-based vs non-platinum combination chemo	12% reduction in risk of death at 1 year with cisplatin-based therapy (OR 0.88, $p = 0.04$)
Adjuvant therapy				
Bria et al.[5]	11 RCT, 1 meta-analysis	6494	Platinum-based chemo vs no chemo after surgery	7% reduction in risk of death with chemotherapy (HR 0.93, $p = 0.01$) 3.1% increase in survival (absolute benefit)

BSC, best supportive care; chemo, chemotherapy; HR, hazard ratio; MST, median survival time; OR, odds ratio; RCT, randomized clinical trial.

reluctant to use it routinely as a result of its toxicity profile. Numerous trials have been conducted in an effort to find alternatives to cisplatin-based therapy that retain its efficacy but reduce toxicity. Again, because no one trial has provided a definitive answer, four groups have conducted meta-analyses to evaluate the specific contribution of cisplatin to the efficacy of combination chemotherapy for NSCLC.[3,4,6,7] In the Japanese study, data from 2948 patients enrolled in eight randomized trials that compared cisplatin-based with carboplatin-based combination chemotherapy were used.[3] Three trials combined the platinum agent with etoposide, mitomycin, vindesine, or vinblastine, all older agents that are no longer recommended in clinical practice guidelines. The remaining five trials utilized new agents: docetaxel, paclitaxel, or gemcitabine. When all trials were included, cisplatin-based therapy was associated with a 5% gain in overall survival ($p = 0.5$); however, when just the results from the trials that utilized new agents were included, the survival benefit with cisplatin doubled (11%; hazard ratio [HR] 1.106, $p = 0.039$). Grade 3/4 nausea and vomiting were significantly more common with cisplatin, whereas grade 3/4 thrombocytopenia was significantly more common with carboplatin. The number of treatment-related deaths was small in both cohorts (3.9 and 2.9%, respectively). The higher risk of treatment-related death with cisplatin-based therapy was not statistically significant (odds ratio [OR] 1.36, 95% confidence interval [CI] 0.89–2.07). Similar results were reported in a comprehensive review of randomized studies in over 2300 patients.[6]

In a similar analysis, cisplatin-based therapy was associated with a 12% reduction in the relative risk of death when compared with non-platinum combination chemotherapy.[5] This meta-analysis included results from 14 randomized trials with 5943 patients. Most trials evaluated doublets and most used one of the newer agents. Statistical heterogeneity related to the inclusion of trials that utilized triplets was detected, and when these trials were excluded, cisplatin-based chemotherapy was associated with a significant reduction in the odds of death at 1 year (OR 0.88, $p = 0.04$). Although toxicity was generally greater with cisplatin-based therapy, there was no difference in the rate of treatment-related mortality. Studies comparing cisplatin-containing regimens with carboplatin regimens, such as the Southwest Oncology Group 9509 trial,[8] found no difference in patient-expressed QoL using the validated FACT-L instrument. All of the above studies were 'literature based' meta-analyses. The first individual patient data-based meta-analysis was recently presented, which investigated this question.[7] This study produced very similar results, showing a highly significant improvement in the response rate in patients randomly assigned to cisplatin regimens compared with carboplatin. As in the Hotta meta-analysis, survival was modestly improved in the cisplatin group, with significant differences seen in those patients receiving third-generation two-agent regimens. Of additional interest is the finding of the similar results determined from both the literature-based and the individual patient data meta-analyses methods.