

ORIGINAL ARTICLE

Systematic analysis of design and stratification for phase III trials in first-line advanced non-small cell lung cancer

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Abstract

Background: A recent study reviewed phase III trials of first-line advanced non-small cell lung cancer (NSCLC) conducted from 1981 to 2010, and provided trends in the study outcome. However, such trials have never been analyzed in detail for design and stratification factors.

Methods: Phase III studies of systemic treatment for first-line advanced or metastatic NSCLC published in English literature between 1981 and 2010 were identified. Characteristics, including sample size, number of trials, region, rate of meeting accrual goal, primary endpoint, type of phase III, interim analysis, allocation method, and stratification factors, were determined for each decade.

Results: A total of 162 studies met the criteria. The number of studies and sample size increased over the three decades. The primary endpoint was reported more frequently in recent decades, and non-overall survival endpoints were chosen in European and Asian studies. Interim analysis was conducted more commonly during the 2000s. Allocation method was rarely reported throughout the three decades. The number of stratification factors increased significantly from one in 1980s to three in 2000s. Performance status, stage, and institution were most frequently selected, and at least one of the three factors was used in most of the studies in the 2000s. However, there are many other stratification factors that were used infrequently.

Conclusions: Despite Consolidated Standards of Reporting Trials guidelines, allocation method has rarely been reported. The choice of stratification factor remains inconsistent across studies.

Introduction

Lung cancer continues to be the leading cause of cancer death in both men and women worldwide. Approximately 159 000 patients die annually in the United States.¹ Non-small cell lung cancer (NSCLC) accounts for the majority of lung cancer cases and its management remains a challenge.² A substantial portion of cases are metastatic disease, which require systemic treatment. Systemic chemotherapy was shown to improve patient survival and quality of life, and, therefore, it became the standard management for stage IV NSCLC.^{3,4}

To establish new treatment regimens, a number of agents have been investigated in clinical trials. Numerous phase III trials and meta-analyses comparing investigational with standard management have been conducted in the field.⁵ The discovery of driver oncogenes and development of targeted

therapy contributed to prolonged survival in patients with epidermal growth factor receptor and anaplastic lymphoma kinase driven NSCLC.^{6–9}

Nevertheless, we have made minimal progress in the overall population. Five-year survival of lung cancer has increased by only 2% over the last few decades.¹ Stage IV NSCLC remains an incurable disease, and most patients die within two years of diagnosis. To determine how the recent phase III studies improved NSCLC management, Sacher *et al.* conducted a review of phase III studies in advanced/metastatic NSCLC.⁵ The review demonstrated that the magnitude of difference in survival between experimental and reference arms has gradually decreased over the decades. They also found that studies from 2001 to 2010 were more frequently reported as positive on the basis of nonsignificant overall survival (OS) or secondary endpoints, such as

progression-free survival (PFS). However, the differences in design and characteristics between decades were not discussed in detail. The number and choice of stratification factors for NSCLC studies have never been discussed in the literature.

In this study, we conducted a thorough review of published phase III studies that were identified in Sacher *et al.*'s analysis. We found that recent studies had larger sample sizes, more frequently defined primary endpoint and accrual goals, and conducted interim analyses. However, we also found that most studies still do not report allocation method. The number of stratification factors used in the studies increased, and stage and institution are increasingly being utilized. Our report will likely contribute to the study design development of future trials.

Methods

In order to identify phase III studies for first-line advanced or metastatic NSCLC, we reviewed a recently published article by Sacher *et al.* that analyzed published phase III studies in advanced NSCLC between 1981 and 2010.⁵ To the best of our knowledge, the article by Sacher *et al.* is the only study that has comprehensively reviewed the literature and provided the list of trials in its supplemental information.

Eligible phase III trials for this analysis must have been conducted for first-line advanced or metastatic NSCLC and have been published in English literature. Randomization must have occurred before the first dose of systemic therapy. Of the 203 articles identified by Sacher *et al.*, one was conducted for small cell lung cancer.¹⁰ Nineteen were conducted primarily in second-line NSCLC, three included a substantial number of previously treated patients, nine were studies on maintenance chemotherapy, seven were duplicated publications, and two were published in non-English language journals.^{11–22}

A total of 162 unique studies for first-line NSCLC were analyzed in detail. Characteristics and design of the studies in each decade were assessed and included number of studies, treatment arms, region, rate of meeting accrual goal, primary endpoint, type of phase III, interim analysis, allocation method, and stratification factors. Of note, reporting the primary endpoint was defined only when the article specifically described the primary endpoint/objective or used the endpoint for estimating sample size.

Studies were defined as international studies if they were conducted in more than one continent. Studies with molecular targeted therapy were compared to those with other agents. All other variables were searched and determined only if clearly defined in the abstract or method section. Type of phase III was classified as superiority, noninferiority, reduction, superiority and noninferiority or unclear. Allocation methods were also sorted into block randomization, minimi-

zation, and unknown. Studies were considered to have used the minimization method if they mentioned minimization or cited any related articles.

All of the identified stratification factors were counted for each study, and then the three most commonly used factors were investigated thoroughly.

Statistics

All of the multi-group non-parametric comparisons were performed with a Kruskal–Wallis test with a statistical significance level of 0.05.

Results

A total of 162 studies in first-line chemotherapy on advanced or metastatic NSCLC were analyzed, as shown in Table 1. The number of studies increased from 29 in 1981–1990, to 46 in 1991–2000, and to 87 in 2001–2010. The median number of enrollments per study increased substantially to over 400 in 2001–2010. The rise in the number of studies is largely attributed to the increase in European and international studies. Recent studies met planned patient accrual likely as a result of more frequent reporting of planned sample size. Contradictory to Sacher *et al.*'s review, our extensive analysis found that the primary endpoint was not well defined in articles in the 1980s. Only 24% of the studies clearly reported study endpoints. The discrepancy is partly because of the exclusion of 41 trials, but perhaps more a result of thorough investigation and the explicit definition of primary endpoint in our review. In the 2000s, the primary endpoint was more clearly defined and most (74%) studies used OS. The remaining studies in the 2000s included other endpoints, such as PFS and overall response rate (ORR). The non-OS primary endpoints were more commonly used in Europe and Asia (Fig 1).

Reporting type of phase III increased from 21% in the 1980s to 77% in the 2000s. Only eight noninferiority studies were conducted in the 2000s: four were performed in Asia, three in Europe, and none in North America. Planned interim analysis was also more frequent in studies in the 2000s. Reporting allocation method, however, remained infrequent over the decades. A majority of studies (78% in all decades) did not report allocation method. Minimization was chosen more frequently in international (4 of 19 studies) and European (16 of 96 studies) studies (data not shown).

The median number of stratification factors significantly increased from one in the 1980s, to two in the 1990s, to three in the 2000s (Table 2, $P = 0.0003$ by Kruskal–Wallis).

The median number of stratifications by region was 3 in North American and international, 2.5 in Asian, and 2 in European studies (data not shown). Performance status (Eastern Cooperative Oncology Group/World Health Organization), stage, and institution were the most commonly

Table 1 Characteristics of studies in three decades

		1981–1990	1991–2000	2001–2010	Total
No. of studies		29	46	87	162
Median no./study		133	181	407	292
Region	North America	14 (48)	4 (9)	14 (16)	32 (20)
	Europe	12 (41)	37 (80)	47 (54)	96 (59)
	Asia	2 (7)	2 (4)	10 (11)	14 (9)
	Others	1 (3)	0	0	1 (0.6)
	International	0	3 (7)	16 (18)	19 (12)
Arms	2 arms	21 (72)	37 (80)	70 (80)	128 (79)
	3 arms	6 (21)	6 (13)	11 (13)	23 (14)
	4 arms	1 (3)	2 (4)	6 (7)	9 (6)
	5 arms	1 (3)	1 (2)	0	2 (1)
	Meeting planned accrual	1 (3)	24 (52)	71 (82)	96 (59)
Primary endpoint	OS	5 (17)	20 (43)	62 (71)	87 (54)
	ORR	0	10 (22)	9 (10)	19 (12)
	PFS/TTP	0	0	6 (7)	6 (4)
	Multiple	2 (7)	6 (13)	0	8 (5)
	Unclear	22 (76)	8 (17)	1 (1)	31 (19)
	QoL	0	1 (2)	4 (5)	5 (3)
	AEs	0	1 (2)	1 (1)	2 (1)
	Clinical benefit	0	0	1 (1)	1 (0.6)
Type of phase III	Superiority	6 (21)	35 (76)	74 (85)	115 (71)
	Noninferiority	0	0	8 (9)	8 (5)
	Reduction	0	0	1 (1)	1 (0.6)
	Superiority & noninferiority	0	0	2 (2)	2 (1)
	Unclear	23 (79)	11 (24)	2 (2)	36 (22)
Interim analysis	Planned	1 (3)	9 (20)	29 (33)	39 (24)
	Not/not reported	28 (97)	37 (80)	58 (67)	123 (76)
	Allocation method				
Allocation method	Minimization	0	7 (15)	16 (18)	23 (14)
	Block randomization	0	3 (7)	9 (10)	12 (7)
	Unclear	29 (100)	36 (78)	62 (72)	127 (78)

First-line studies in advanced NSCLC were selected from the study list provided by Sacher *et al.* Studies that were duplicated, included previously treated patients or were published in non-English literature were excluded. International studies were defined if conducted in more than one continent. Percentages are shown in parentheses. AEs, adverse events; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TTP, time to progression.

reported stratification factors in all three decades. Stage and institution were chosen more frequently in recent studies. Most studies (84%) in the 2000s used at least one of the three factors.

However, there are a number of stratification factors that were reported infrequently: histology (24 studies), gender (16), weight loss (14), brain metastasis (10), age (9), measurable disease (9), prior therapy (8), region (7), lactate dehydrogenase (5), response to pre-randomization chemotherapy (1 randomized after 2 cycles of chemotherapy), albumin (2), histologic versus cytologic diagnosis (1), metastasis in bone/liver/brain (1), metastatic sites (1), neutrophil count (1), Charlson score (1), chemotherapy regimen to be used (1), smoking (1), and symptom (1).

Studies using molecular targeted agents were analyzed as a special population of interest. A total of 14 studies with target agents were identified, in the 2000s only. Four of the 14 studies (29%) reported minimization methods, whereas 12

studies (86%) used performance status, stage or institution. The median number of stratification factors in these studies was identical to that in other studies in the 2000s, indicating no distinct trend when compared to the overall population.

Discussion

Randomized phase III trials and meta-analyses have been considered an excellent methodology to determine if the investigational approach is superior to control. They have been heavily cited and referenced by physicians who make clinical decisions. A number of such studies have been conducted in the oncology field. Recently Sacher *et al.* conducted an extensive review of phase III trials for metastatic NSCLC.⁵ They primarily focused on change in patient survival over three decades; however, the trend in study design has never been assessed in the literature. To the best of our knowledge, our analysis is the first study to thoroughly analyze details of

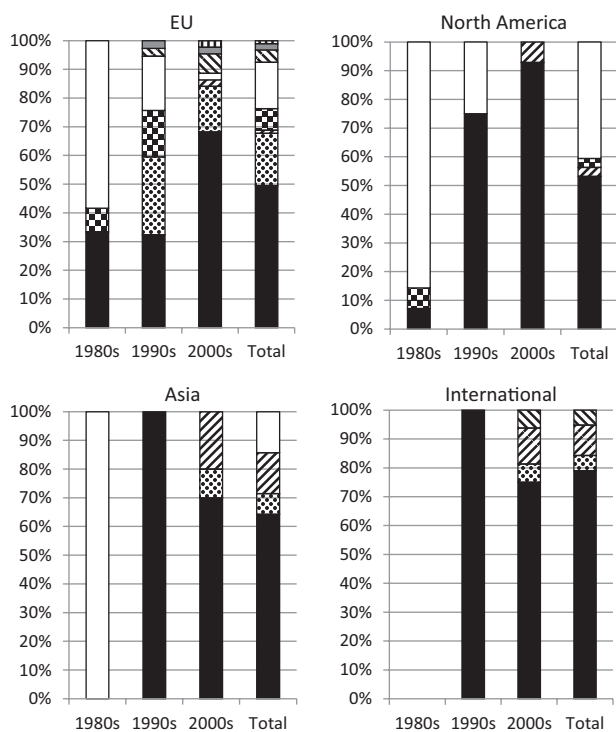


Figure 1 Differences in primary endpoint by decades and regions. Studies that were conducted in multiple continents were defined as international. Most studies in the 1980s did not report a primary endpoint. There was no international study in the 1980s. AEs, adverse events; EU, European Union; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TTP, time to progression. Clinical benefit, □; AEs, ■; QoL, ▨; unclear, ▩; multiple, ▤; PFS/TTP, ▧; ORR, ▨; OS, ■.

study designs in phase III studies of first-line NSCLC. There has been a substantial increase in the number of trials and enrolled patients over three decades. This increase is largely attributed to the concomitant increase in European and international studies. This finding may further promote additional international studies.

Recent studies have had clearly defined primary endpoints more frequently than older studies, with OS as the most common primary endpoint of choice. Non-OS end points, such as PFS, time to progression, and ORR have occasionally been selected in European and Asian studies. Reporting the type of phase III design has increased over the decades, with the superiority design remaining the dominant type. There have been several international noninferiority studies, but North America did not use the noninferiority design during the three decades. Interim analysis has also been more frequently planned, though it accounts for only a third of the studies in the 2000s.

Allocation methods are infrequently reported in the published literature of NSCLC phase III studies. The Consolidated Standards of Reporting Trials (CONSORT) guidelines were initially established in 1996 in order to provide guidance on how to report phase III studies in medical research.²³ It clearly defined that allocation methods be reported as part of methodology. Despite the CONSORT guidelines being adopted by thousands of journals, many studies do not report allocation methods.²³ Although there is a trend in increased reporting, only 28% of studies reported allocation methods in the 2000s.

Stratification factors are presumed prognostic factors that can influence outcome and potentially cause an imbalance among each treatment arm, and, therefore, have been commonly used in randomized studies.²⁴ Nevertheless, the choice and number of stratification factors have never been standardized or even systematically assessed for NSCLC studies. This study found that inconsistency exists in choice and number, suggesting an unfavorable influence on meta-analyses if conducted. Variability in selection of stratification factors was also observed in meta-analyses of gastric and colorectal cancer studies.^{25,26} However, the most commonly used factors identified in the present systemic analysis were performance status, stage, and institution. An increase in the number of stratification factors make studies more complex, and, therefore, is not always

Table 2 Stratification factors in first-line phase III NSCLC trials

	1981–1990	1991–2000	2001–2010	Total
No. of studies	29	46	87	162
Median no. of SFs	1	2	3	2
PS	14 (48)	21 (46)	48 (55)	83 (51)
Stage	2 (7)	22 (48)	63 (72)	86 (53)
Institution	2 (7)	17 (37)	37 (43)	56 (35)
PS or stage	15 (52)	29 (63)	6 (7)	113 (70)
PS, stage or institution	16 (55)	32 (70)	73 (84)	121 (75)
Not reported or none	12 (41)	13 (28)	13 (15)	38 (23)
All others	1 (3)	1 (2)	1 (1)	3 (2)

The median number of stratification factors (SF) increased significantly (one way analysis of variance, $P = 0.003$). All others, SF other than performance status (PS), stage, and institution. NSCLC, non-small cell lung cancer.

recommended. Kernan *et al.* suggested that stratification is needed if the sample size per arm is below 200 for superiority studies, if they are noninferiority studies, or if an interim analysis is planned.²⁷ Of the studies in this review, 75% used at least one of the three factors, whereas only 2% chose different factors. We need to avoid complexity and maintain consistency from the studies in previous years. Unless they are definitively prognostic, we would not recommend selecting factors other than performance status, stage, and institution.

We must acknowledge the limitation of this study. Because of a dependence on published studies in the English literature, publication biases might exist. Unpublished studies might have indispensable information. Underreporting of any variables in the published studies may also affect the analysis, and we believe this would have been more likely to occur in the 1980's studies.

Conclusion

In conclusion, the current analysis found substantial change in the design and reporting of phase III trials of first-line metastatic NSCLC. Our review of stratification factors will provide future researchers with valuable information when they design trials.

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Disclosure

No authors report any conflict of interest.

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