Original Article

Gemcitabine-based Doublets Versus Single-agent Therapy for Elderly Patients With Advanced Nonsmall Cell Lung Cancer

A Literature-based Meta-analysis

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BACKGROUND: Although platinum-based combinations are considered the best option of care for patients with advanced nonsmall cell lung cancer (NSCLC), single-agent therapy is the preferred treatment for older patients. Since the late 1990s, various combinations of third-generation agents (gemcitabine [G], vinorelbine, docetaxel, and paclitaxel) have been tested, yielding contradictory results. The authors of this report performed a literature-based meta-analysis to assess the efficacy and tolerability of G-based doublets compared with single-agent chemotherapy for elderly patients with NSCLC. **METHODS:** Data from all published, randomized, phase 3 trials that compared a G-based doublet with a third-generation single agent in elderly patients were collected from electronic databases (Medline and the Cochrane Central Register of Controlled Trials), relevant reference lists, and abstract books. Pooled odds ratios (ORs) were calculated for the 1-year survival rate, the overall response rate (ORR), and grade 3 and 4 toxicities. **RESULTS:** Four eligible trials (1436 patients) were selected from 442 studies that initially were identified. A significant difference in ORR favoring G-based doublets over single agents was observed (OR, 0.65; 95% confidence interval [95% CI], 0.51-0.82 [$P < .001$]), whereas the trend toward an improved 1-year survival rate was not significant (OR, 0.78; 95% CI, 0.57-1.06 [$P = .169$]). Grade 3 and 4 toxicities did not differ significantly except for thrombocytopenia (OR, 1.76; 95% CI, 1.12-2.76 [$P = .014$]). **CONCLUSIONS:** G-based doublets appeared to be effective and feasible compared with single agents in the treatment of elderly patients with advanced NSCLC who were not suitable for full-dose, platinum-based chemotherapy. Further prospective, elderly specific, phase 3 trials will be necessary. **Cancer 2009;115:1924–31. © 2009 American Cancer Society.**

KEY WORDS: nonsmall cell lung cancer, advanced, elderly, gemcitabine, doublet regimen, meta-analysis.

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The standard treatment for elderly patients with advanced nonsmall cell lung cancer (NSCLC) remains a matter of debate. Although the median age at diagnosis is 70 years,[1] elderly patients with cancer are under-represented in clinical trials, mainly because of protocol exclusion criteria.[2,3]

The physiologic decline associated with aging may affect chemotherapy-induced toxicities. However, chronologic age alone cannot address individual patient management.[4] Several reports have remarked that a comprehensive geriatric assessment (CGA) may help identify those older individuals who are *fit* and are more likely to benefit from standard cancer treatment compared with those who are *vulnerable* and need tailored chemotherapy regimens or those who are *frail* and are candidates for supportive care only.[5] Consequently, the inclusion of CGA in studies designed for elderly patients is strongly recommended.[6]

Because of the selection of a favorable subset of elderly patients who can tolerate cancer treatment better, older patients enrolled in clinical trials are less likely to be representative of the whole elderly population, so that considerable caution is needed when collecting data from retrospective analyses of phase 3 randomized trials.[7] Although the response rate and the survival rate (SR) among elderly patients with NSCLC who receive platinum-based therapy are similar to those among younger patients,[8-10] such treatment should be considered only for *fit* patients until ongoing elderly specific trial results are presented.[11]

Available data regarding the efficacy and tolerability of current chemotherapy regimens in the treatment of elderly patients with advanced NSCLC indicate that no specific regimen can be regarded as the standard therapy except third-generation single agents.[12,13] In the phase 3 Elderly Lung Cancer Vinorelbine Italian Study, vinorelbine compared with best supportive care alone demonstrated a significant advantage in terms of the median overall survival and better quality-of-life scores.[14] Gemcitabine and taxanes also were studied extensively as single-agent chemotherapy regimens and demonstrated both activity and tolerability in prospective phase 2 and 3 trials.[15-17] Specifically, a 3-week schedule of docetaxel compared with vinorelbine improved progression-free survival (PFS), the overall response rate (ORR), and cancer-related symptoms but was associated with higher rates of grade 3 and 4 neutropenia.[18] To improve on the results obtained with single third-generation agents, nonplatinum third-generation doublets, such as gemcitabine-vinorelbine or gemcitabine-taxanes, were evaluated and yielded contradictory results with regard to response and SRs.

MATERIALS AND METHODS

Objective of the Current Study

The current literature-based meta-analysis was performed to evaluate the efficacy (1-year SR and ORR) and the toxicity profile of third-generation doublets compared with third-generation single agents for the first-line treatment of elderly patients with stage IIIB/IV NSCLCs.

Criteria for Selecting Studies

Only published, randomized phase 3 trials that evaluated the benefit of adding a second third-generation drug to a third-generation single agent in untreated elderly patients with advanced NSCLC were selected. Because the definition of elderly based on calendar age remains unclear, and no cutoff age has been established to date, the age of patients enrolled in elderly specific trials may vary. We performed an electronic search using the medical subject headings (MeSH) term "*aged, elderly*," which indicates individuals ages 65 through 79 years.

Search Strategy

A thorough bibliographic electronic search of MEDLINE (from 1966 to September 2008) and the Cochrane Central Register of Controlled Trials was conducted. The following search terms were used: "*randomized*," "*phase III*," "*NSCLC*," "*carcinoma, non-small-cell lung/drug therapy*" (MeSH), "*carcinoma, non-small-cell lung/secondary*" (MeSH), "*elderly,*" "*aged*" (MeSH), and "*antineoplastic combined chemotherapy protocols*" (MeSH). The search was limited to trials that were randomized, controlled, and published in the English language (*English* [lang] *AND randomized controlled trial* [ptyp]). The results were supplemented with manual searches of American Society of Clinical Oncology meeting proceedings, references of selected articles, and published reviews. When an abstract from a meeting and a full article referred to the same trial,

only the full article was evaluated. When 2 or more articles reported the same data, the most recently updated data were included.

Definition of Outcomes

Efficacy was assessed using 1-year SR as the primary outcome and ORR as the secondary outcome. The 1-year SR is defined as the percentage of patients who remain alive 1 year after randomization, and the ORR is the percentage of patients who have a complete or partial tumor response according to World Health Organization criteria. Regarding toxicity, we considered both hematologic (anemia, neutropenia, thrombocytopenia) and nonhematologic (nausea and vomiting) grade 3 and 4 side effects of treatment.

Data Extraction

Two independent reviewers extracted data by filling in an appropriate form. Mismatches between reviewers were resolved through an independent review by a third investigator. The following data were collected from the identified trials: first author name, journal and year of publication, age of patients, drugs used and administration doses, number of patients, 1-year SR, ORR, and percentage of patients who experienced grade 3 and 4 toxicities.

Statistical Analysis

Data from selected trials were analyzed using NCSS software (2007 version; Kaysville, Utah). The doublet was considered an investigational treatment, and the single agent was used as a control treatment. When a trial compared >2 different chemotherapy regimens, the investigational or control arm was counted twice or more in the analysis, so that the number of comparisons was greater than the number of included trials.

The outcomes were represented by dichotomous variables: The 1-year SR was calculated by applying an intent-to-treat analysis; ORR and grade 3 and 4 toxicity analyses were performed by considering the number of patients evaluable for response and toxicity, respectively. The differences in efficacy and toxicity between treatment arms were standardized through odds ratios (ORs) of an "event" for each treatment outcome. We considered the following as "events": for the 1-year SR, death; for the ORR, nonresponse; for grade 3 and 4 adverse effects, toxicity. We also calculated 95% confidence interval (95% CI) for each. The ORs were significant when the value 1 was not within the 95% CI. ORs <1.0 indicated a benefit of the doublet over the single agent and, consequently, a higher SR, a higher response rate, and less toxicity. A pooled OR for each outcome was computed by using fixed-effects or random-effects models according to the Mantel-Haenszel method. The heterogeneity between trials was tested using the Cochran Q test. To allow an easier interpretation of the results, the difference in risk between investigational and control arms was calculated.

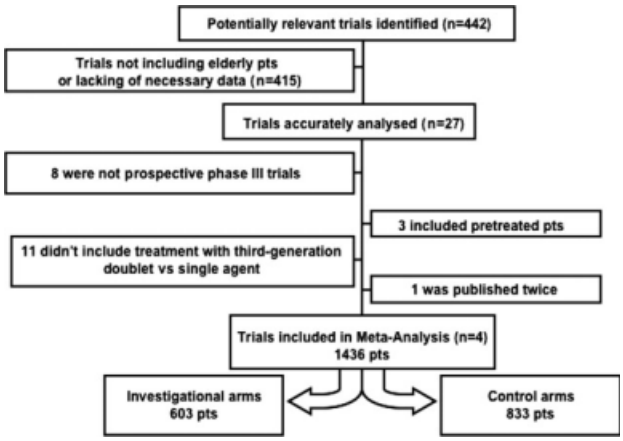

FIGURE 1. The flow-chart of selected trials. Pts indicates patients.

RESULTS

From the 442 potentially relevant trials, 414 trials were considered ineligible because they did not include elderly patients, and 1 trial was ineligible because no detailed data were available. The remaining 27 trials were analyzed accurately, and 23 were excluded from meta-analysis (8 were not phase 3 trials, 3 included pretreated patients, 11 did not include treatment with a third-generation doublet versus a single agent, and 1 was published twice). A full description of the ineligible and excluded trials is available from the authors on request. After the selection procedure, 4 trials[16,19-21] that included 1436 patients (603 in the investigational arms and 833 in the control arms) were analyzed (Fig. 1). The lower age limit was 65 years in only 1 of the 4 trials that were included and 70 years in the remaining 3 trials. Because several trials had >2 eligible

Table 1. Characteristics of the 4 Randomized Phase 3 Trials Included in the Meta-Analysis

Reference	Treatment Arm (Dose, mg/m^2)	Schedule	No. of Patients	Age, y	OS, wk	1-y SR, %	ORR, %
Frasci 2001[20]	G (1200)+V (30)	D1+8 every 21 d	60	≥70	29	30	22
	V (30)		60		18	13	15
Gridelli 2003[16]	G (1000)+V (25)	D1+D8 every 21 d	232	≥70	30	30	21
	G (1200)		233		28	28	16
	G (1000)+V (25)	D1+D8 every 21 d	232		30	30	21
	V (30)		233		36	38	18
Comella 2004[19]	G (1000→1200)+V (25→30)	D1+D8 every 21 d	68	≥70	9.7	32	23
	G (1200→1400→1600)	D1,D8,+D15 every 28 d	68		5.1	29	18
	G (1000→1200)+V (25→30)	D1+D8 every 21 d	68		9.7	32	23
	P (100→120→140)	D1,D8,+D15 every 28 d	63		6.4	25	13
	G (1000→1200) +P (80→100)	D1+D8 every 21 d	65		9.2	44	32
	G (1200→1400→1600)	D1,D8,+D15 every 28 d	68		5.1	29	18
	G (1000→1200)+P (80→100)	D1+D8 every 21 d	65		9.2	44	32
	P (100→120→140)	D1,D8,+D15 every 28 d	63		5.1	25	13
Hainsworth 2007[21]	G (800)+D (30)	D1,D8,+D15 every 28 d	174	>65	5.5	26	25
	D (36)		171		5.1	24	17

OS indicates overall survival; 1-y SR, 1-year survival rate; ORR, overall response rate; G, gemcitabine; V, vinorelbine; →, dose escalation; P, paclitaxel; D, docetaxel.

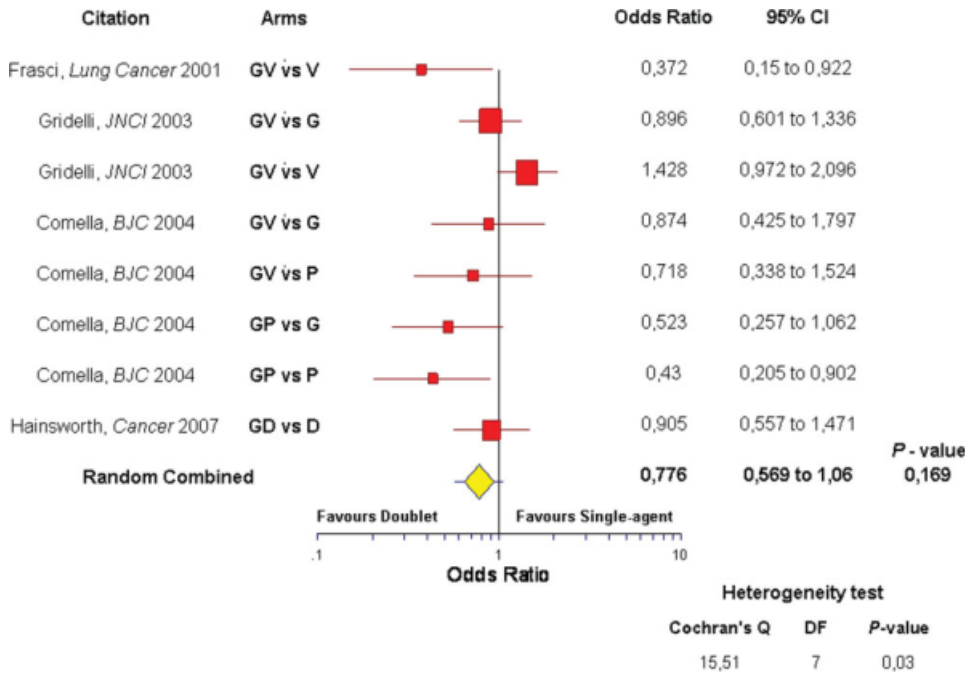

FIGURE 2. Comparison of the 1-year survival rate between doublet arms and single-agent arms of all identified, assessable trials. 95% CI indicates 95% confidence interval; G, gemcitabine; V, vinorelbine; *JNCI*, *Journal of the National Cancer Institute*; *BJC*, *British Journal of Cancer*; P, paclitaxel; D, docetaxel; DF, degrees of freedom.

arms, the number of comparisons was 8 (1923 patients). Drug doses, schedules, number of patients in each arm, age of patients in each trial, and outcomes (OS, 1-year SR, and ORR) for all 4 trials are reported in Table 1. All necessary data were available in all studies.

In the pooled analysis, doublets were associated with a nonstatistically significant increase in the 1-year SR (OR, 0.78; 95% CI, 0.57-1.06 [$P = .169$]) (Fig. 2). The random-effects model for calculating OR of death was used because of significant heterogeneity ($P = .03$).

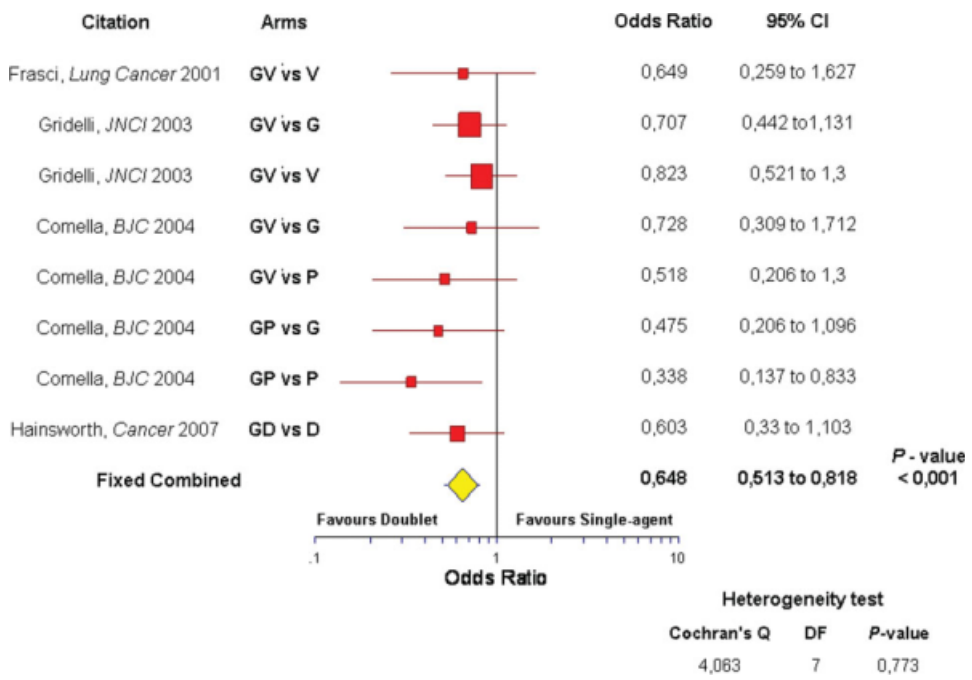

FIGURE 3. Comparison of the overall response rate between doublet arms and single-agent arms of all identified, assessable trials. 95% CI indicates 95%confidence interval; G, gemcitabine; V, vinorelbine; *JNCI*, *Journal of the National Cancer Institute*; *BJC*, *British Journal of Cancer*; P, paclitaxel; D, docetaxel; DF, degrees of freedom.

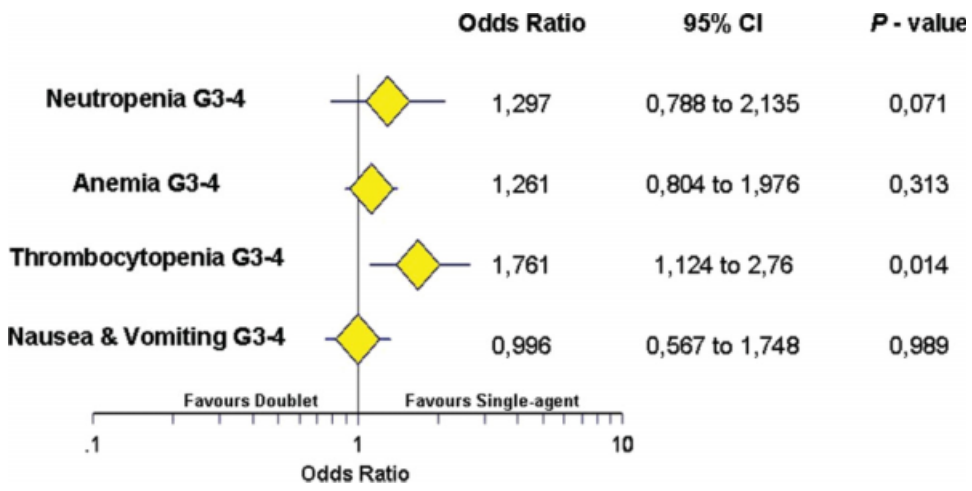

FIGURE 4. Odds ratios of grade 3 and 4 (G3-4) toxicities. 95% CI indicates 95% confidence interval.

A statistically significant increase in the ORR favoring doublets was observed (OR, 0.65; 95% CI, 0.51-0.82 [$P < .001$]) (Fig. 3). The pooled OR for nonresponse was calculated using the fixed-effects model because of the lack of heterogeneity ($P = .77$). Gemcitabine-containing combinations demonstrated a 6.9% reduction in the risk of nonresponse. Slight increases in thrombocytopenia (OR, 1.76; 95% CI, 1.12-2.76 [$P = .014$]), but no grade 3 or 4 hematologic or nonhematologic toxicities, were associated significantly with gemcitabine-based doublets (Fig. 4).

DISCUSSION

In this retrospective subgroup analyses of studies that used platinum combination chemotherapy, the selected elderly patients who were eligible for aggressive treatment, who

represented a minority of the study population, had outcomes similar to those achieved by their younger counterparts with acceptable hematologic and nonhematologic side effects.[8-10] The age-related reduction in the functional reserve of many organs and/or comorbidities may contraindicate cisplatin-based regimens in nonselected elderly patients because of concern regarding patients' tolerability. Cisplatin has a low therapeutic ratio with significant toxicities, including nausea and vomiting, renal function impairment requiring adequate hydration, ototoxicity, and neuropathy. Carboplatin administration causes lower rates of nonhematologic side effects, although it produces more profound myelosuppression, especially in combination with other myelotoxic agents.[22]

Single-agent chemotherapy (gemcitabine, vinorelbine, or taxanes) was studied first and is the approach preferred by several oncologists for the treatment of nonselected elderly patients with advanced NSCLC.[12,13] To minimize chemotherapy-induced myelosuppression, weekly schedules have been investigated in many studies, especially when taxanes were administered. We planned the current meta-analysis to evaluate whether third-generation doublets could provide better results than single agents without the increased occurrence of severe toxicities.

The heterogeneity in data regarding age and elderly assessment among the reviewed studies reflects the selection bias of the available elderly specific, randomized phase 3 trials. In 2 of the selected studies,[19,21] patients with poor performance status were included together with elderly patients, leading to a heterogeneous study population. Overall, a bad performance status predicts worse survival.[23] This selection bias should not particularly affect our findings because of the small percentage of younger patients who had a performance status of 2 among those enrolled in these studies.

Unfortunately, none of the studies that were analyzed in this meta-analysis reported whether CGA was used to evaluate the elderly patients on study before enrollment, although this may support the generalizability of our results to an unselected elderly population. In performing a meta-analysis based on published data, only the issues investigated by the authors can be analyzed. Furthermore, all of the selected trials started when CGA was not used routinely in clinical practice.

Because of its favorable toxicity profile, its proven efficacy, and its synergistic action with other third-generation agents, gemcitabine was chosen for third-generation combination regimens in randomized phase 3 trials that were dedicated to elderly patients with advanced NSCLC. It is noteworthy that all of the platinum-free combinations that were selected for this meta-analysis contained gemcitabine.

Even if contradictory results were reported from prospective trials that compared third-generation doublets and single agents, our meta-analysis indicates a significantly increased response rate with gemcitabine-based regimens over single-agent chemotherapy and a clear trend toward an improved 1-year SR, although the latter improvement missed statistical significance. A possible explanation for the lack of significance in the 1-year SR may rely on the use in the largest study of 20% lower doses of gemcitabine and vinorelbine in combination compared with the doses administered in the other studies that tested the same doublet. It is possible that, with more homogeneous dosages and larger samples, a significant result may have been achieved.

With regard to tolerability, only data on hematologic toxicities and nausea and vomiting were available, so that no definitive conclusion could be drawn. The rate of severe hematologic toxicities, as expected, increased when a second drug was added to gemcitabine, but only grade 3 and 4 thrombocytopenia was associated significantly with doublet regimens.

The analysis of available literature performed for this review confirmed the absolute urgency of prospective randomized clinical trials dedicated to elderly patients with NSCLC to guide therapeutic decisions. Further trials comparing platinum-based and nonplatinum-based regimens in the elderly already are ongoing and are using adapted doses and schedules to obtain an effective and well tolerated treatment.

With regard to the administration of new drugs, the available data from retrospective subset analyses of large randomized trials do not support their ordinary use. Bevacizumab does not appear to be particularly suitable for elderly patients, because it may be too toxic[24]; whereas pemetrexed and erlotinib, although they demonstrated similar survival and toxicity rates between older and younger patients, were studied in a highly selected patients who had received previous platinum-based chemotherapy and were eligible for second-line therapy.[25,26]

Although our analysis suggests that gemcitabine-based doublets should be considered for first-line chemotherapy for such elderly populations, it must be taken into account that an overestimation of treatment effects is possible when a meta-analysis is not based on individual patient data. Performing a meta-analysis using individual patient data certainly would have provided more rigorous results, even if it would have required greater human, material, and perhaps financial means.

Conflict of Interest Disclosures

The authors made no disclosures.

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