Pooled Analysis of Elderly Patients with Non-small Cell Lung Cancer Treated with Front Line Docetaxel/Gemcitabine Regimen: The Hellenic Oncology Research Group Experience

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Introduction: Thirty to 40% of patients with non-small cell lung cancer (NSCLC) are older than 70 years and rarely are enrolled in clinical trials. Moreover, in clinical practice, >75% of patients older than 65 years with metastatic NSCLC never receive any kind of chemotherapy.

Purpose: To retrospectively evaluate the impact of age on efficacy and toxicity of chemotherapy regimens in patients with advanced NSCLC treated with the docetaxel-gemcitabine combination.

Patients and Methods: Pooled data from six clinical trials of the Hellenic Oncology Research Group were analyzed. According to their age, patients were divided into two groups: those with age <70 years and those with ≥70 years.

Results: A total of 858 patients were included in this analysis. Six hundred sixty-six (77.6%) patients were younger than 70 years, whereas 192 (22.4%) patients where ≥70-year-old. Overall response rate was 30.3% and 30.2% for patients <70 years and ≥70 years, respectively ($p = 0.974$). The median time to tumor progression was 4.1 and 4.5 months for patients <70 years and ≥70 years, respectively ($p = 0.948$). Median overall survival was 9.9 and 9.2 months for patients <70 and ≥70, respectively ($p = 0.117$). The multivariate analysis revealed performance status (PS) ($p = 0.0001$) and stage ($p = 0.0001$) as independent factors with significant impact on the hazard of death. Chemotherapy was well tolerated, but the incidence of grade III/IV mucositis was significantly higher in elderly patients (0.2% versus 1.5% for patients <70 versus ≥70 years, respectively; $p = 0.011$).

Conclusion: The docetaxel/gemcitabine regimen has a comparable efficacy and tolerance in young (<70 years) and elderly (≥70 years) patients.

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Disclosure: The authors declare no conflict of interest.

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ISSN: 1556-0864/08/0305-0505

Key Words: NSCLC, elderly, docetaxel, gemcitabine.

(*J Thorac Oncol.* 2008;3: 505–510)

Non-small cell lung cancer (NSCLC) accounts for 80% of the 170.000 new cases of lung carcinoma diagnosed each year in the United States and remains the leading cause of cancer-related death in Western countries.[1] Surgery remains the only curative treatment modality of patients with NSCLC, but although one-third of them have resectable disease upon diagnosis, less than 5% of the patients are expected to be alive at 5 years.[2,3]

About 50% of newly diagnosed cases of NSCLC concern patients older than 65 years, whereas 30 to 40% of cases are diagnosed in patients older than 70 years.[4] Data from the Surveillance, Epidemiology, and End Results indicate that the median time at diagnosis in NSCLC patients is 69 years.[5] Furthermore, recent data suggest that during the last decade, the incidence and mortality of NSCLC has decreased in younger patients, whereas it has increased among older patients.[6] On the basis of these observations, it becomes clear that NSCLC represents a significant health problem in elderly patients. However, elderly patients are frequently underrepresented in clinical trials evaluating new treatments in NSCLC.[7] Indeed, more than 75% of patients older than 65 years with metastatic NSCLC never receive any kind of chemotherapy in the daily clinical practice.[8]

For over 10 years cisplatin-based chemotherapy represents the cornerstone treatment for advanced NSCLC. A large meta-analysis of eight randomized trials including 778 patients of cisplatin-based chemotherapy compared with best supportive care, demonstrated an advantage of chemotherapy with a 27% reduction in risk of death, and an increase in 1-year survival rate of 10%.[9] On the other hand, the toxicity of cisplatin remains a serious clinical problem. Nausea and emesis are often severe and delayed, and neurotoxicity, renal toxicity and ototoxicity are significant and dose-related.

Moreover, an important proportion of elderly NSCLC patients have significant concomitant cardiac or cardio-respiratory diseases and, thus, there may be a contraindication for the administration of cisplatin. Several randomized phase III trials have demonstrated that non-platinum doublets offer a comparable benefit in terms of time to tumor progression (TTP) and overall survival (OS) and therefore are considered as an alternative therapeutic option, especially in elderly patients with advanced/metastatic NSCLC.[10–12]

In elderly patients, clinical trials have clearly demonstrated that single-agent chemotherapy offers a survival benefit, compared with best supportive care.[13] Regarding combination therapy published results are conflicting and it is not clear whether combination therapy offers benefit compared with monotherapy or not.[14,15] To evaluate the impact of age on efficacy and toxicity of combination regimens we retrospectively reviewed data from six clinical trials[10,11,16–18] of patients with advanced NSCLC treated with the docetaxel-gemcitabine combination as first line treatment. All patients' data were derived from our clinical trials department database.

PATIENTS AND METHODS

Patients

This analysis pooled data from six clinical trials[10,11,16–18] conducted by the Hellenic Oncology Research Group. Patients participating in these trials had locally advanced or metastatic (stage IIIB–IV) NSCLC and a World Health Organization PS of 0–2; all patients had received front-line treatment with the docetaxel/gemcitabine (DG) regimen. All patients gave written informed consent to participate in these studies and the trials were approved by the Ethics and Scientific Committees of the participating centers. All studies were conducted according to the Helsinki Declaration and Good Clinical Practice guidelines.

Fifty-one chemotherapy-naive patients with NSCLC treated with gemcitabine 900 mg/m^2 on days 1 and 8 and docetaxel 100 mg/m^2 on day 8, every 3 weeks were included in a phase II study, assessing the efficacy of the DG combination, as first line treatment in NSCLC.[16]

Another multicenter phase II study enrolled 121 patients with lung adenocarcinomas who received gemcitabine 1100 mg/m^2 on days 1 and 8 plus docetaxel 100 mg/m^2 on day 8, every 3 weeks as first line therapy (unpublished data).

A multicenter randomized phase III trial compared the efficacy of front-line cisplatin/docetaxel and DG combination in patients with advanced NSCLC.[10] Two hundred twenty-two patients were treated with gemcitabine (1100 mg/m^2, days 1 and 8) and docetaxel (100 mg/m^2, day 8), every 3 weeks. No significant differences were observed between the two arms in terms of overall response rate (ORR), TTP, and OS.

Another multicenter, randomized phase III trial compared the activity and tolerability of DG and vinorelbine/cisplatin regimens in chemotherapy-naive NSCLC patients.[11] One hundred ninety-seven patients were assigned to the DG arm (gemcitabine 1000 mg/m^2, days 1 and 8; plus docetaxel 100 mg/m^2, day 8, every 3 weeks). Similarly, this trial also failed to demonstrate any ORR, TTP, or OS difference between the two arms.

Furthermore, docetaxel monotherapy was compared with DG doublet in the context of a randomized multicenter phase III trial.[17] One hundred eighty-six patients in the DG arm received gemcitabine 1000 mg/m^2 on days 1 and 8 plus docetaxel 100 mg/m^2 on day 8 every 3 weeks. A significantly higher ORR (26.8% versus 11.6%, $p < 0.001$) and OS (9.4 months versus 8.3 months, $p = 0.037$) was observed in favor of the doublet, while there was a trend towards a higher TTP in patients receiving the combination regimen.

Finally, a randomized multicenter, phase III study compared oral vinorelbine/gemcitabine combination with the DG combination.[18] Gemcitabine was administered at a dose of 1000 mg/m^2 on days 1 and 8 and docetaxel at a dose of 75 mg/m^2 on day 8. Although a significantly higher ORR was observed with the DG combination (23% versus 11%, $p = 0.018$), there was no difference between the two arms in terms of TTP and OS.

In all but one study, docetaxel was administered at the dose of 100mg/m^2 every 3 weeks and in all studies patients received prophylactic G-CSF support to minimize the incidence of severe and/or febrile neutropenia associated with the high docetaxel dose. This attitude was decided to be followed based on the results of our initial phase II study which was one of the first to report the DG combination in NSCLC.[16] Moreover, in all studies, the administered doses of gemcitabine were ranged from 900 to 1100 mg/m^2. Therefore, patients from all these trials were pooled together, because inclusion criteria were similar, all chemotherapy regimens were similarly administered on days 1 and 8 and, almost, with similar doses, and furthermore, prophylactic administration of G-CSF was stipulated by all trials.[10,11,16–18]

Statistical Analysis

According to their age, patients were divided into two groups: those with age <70 years and those with ≥70 years. Descriptive statistics for the patient group are reported as mean, median, and range. Statistical comparisons between group rates (proportions) were assessed by Pearson's χ^2-test.[19] Differences between groups in terms of survival data were assessed by the log rank and Wilcoxon test (Kaplan-Meier analysis).[20] OS was the primary end point of this analysis. OS was measured from entry into the study until death and the 1-year survival was estimated using the Kaplan-Meier method; the time to disease progression was measured from the enrollment to the study until the day of the first evidence of disease progression. The duration of response was calculated from the day of the first documentation of response to disease progression.

RESULTS

Patients

A total of 858 patients were included in this analysis. Six hundred sixty-six patients (77.6%) were younger than 70 years, whereas 192 (22.4%) patients where ≥70 years old. Patients' characteristics for the two age groups are presented in Table 1. Most patients were men with stage IV NSCLC.

Treatment

The median number of administered cycles was 4 per patient for both groups. The median dose density for docetaxel

TABLE 1. Patients' Characteristics According to Age

	Age <70 (*n* = 666)		Age ≥70 (*n* = 192)		
	No	%	No	%	*p*
Age, yr, median (range)	60 (34–69)		72 (70–78)		
Sex					0.202
Male	577	86.6	173	90.1	
Female	89	13.4	19	9.9	
Stage					0.204
IIIB	197	29.6	66	34.4	
IV	469	70.4	126	65.6	
Histology					0.737
Squamous	313	47.0	96	50.0	
Adeno ca	330	49.5	89	46.4	
Unknown	23	3.5	7	3.6	
PS					0.195
0 + 1	604	90.7	168	87.5	
2	62	9.3	24	12.5	

PS, performance status.

and gemcitabine was 29.0 mg/m^2/wk and 616 mg/m^2/wk, respectively, for patients aged <70 years old. For elderly patients, the median dose density was 29.9 mg/m^2/wk and 613 mg/m^2/wk for docetaxel and gemcitabine, respectively ($p = 0.281$ and $p = 0.899$ for docetaxel and gemcitabine, respectively). A dose reduction was done in 141 (21.2%) patients aged <70 years old, whereas for patients aged ≥70 years, dose reduction was necessary for 46 (24%) ($p = 0.410$). Hematological toxicity was the reason for dose reduction in 39 (27.7%) patients aged <70 and 14 (30.4%) patients aged ≥70-year-old; nonhematological toxicity was the reason for dose reduction in 41 (29.1%) patients aged <70 years and 13 (28.3%) patients aged ≥70 years ($p = 0.780$). Toxicity was the reason for treatment discontinuation in 39 (5.9%) patients aged <70 years and 14 (7.3%) patients aged ≥70 years ($p = 0.467$).

Response to Treatment

There was no difference in terms of complete response rate between the two groups (1.4% for patients aged <70 years versus 1.6% for patients aged ≥70 years; $p = 0.740$). The activity of the DG regimen in the two age groups is presented in Table 2. ORR was 30.3% and 30.2% for patients aged<70 years and ≥70 years, respectively ($p = 0.974$). Median response duration was 6.1 and 5.3 months for the <70 years and ≥70 years patients' groups ($p = 0.060$).

Time to Tumor Progression

The median TTP was 4.1 and 4.5 months for patients aged <70 years and ≥70 years, respectively ($p = 0.948$; Table 3). Univariate analysis including age (≥70 years, <70 years), PS (0–1 versus 2), stage (IIIB versus IV), histology (adenocarcinoma versus squamous), and sex (male versus female), revealed that stage of the disease was the only factor with a significant impact on TTP. Furthermore, a proportional hazards (Cox) regression analysis also revealed that stage of the disease had a significant effect on the hazard of relapse

TABLE 2. Response Rate According to Age Group

	<70 (*n* = 666)	≥70 (*n* = 192)	*p*
CR	9 (1.4%)	3 (1.6%)	0.740
PR	193 (27.1%)	55 (28.6%)	0.732
Overall response rate (CR + PR)	202 (30.3%)	58 (30.2%)	
95% CI	24.53–32.55%	27.84–37.38%	0.974
SD	171 (25.7%)	56 (29.2%)	0.300
PD	293 (43.9%)	78 (40.6%)	

CR, complete response; PR, partial response; CI, confidence interval; SD, stable disease; PD, partial disease.

TABLE 3. Time to Tumor Progression and Overall Survival According to Age Group

	<70 (*n* = 666)	≥65 (*n* = 192)	*p*
TTP			0.948
Median (range) (mo)	4.1 (0.5–66.4)	4.5 (0.5–36.9)	
95% CI	3.53–4.60	3.89–4.97	
1-yr without progression	14.4%	17.6%	
OS			0.117
Median (range) (mo)	9.9 (0.5–90.4)	9.2 (0.5–115.4)	
95% CI	9.12–10.61	7.59–10.81	
1-yr survival	40.7%	39.4%	
2-yr survival	17.0%	10.4%	

TTP, time to tumor progression; CI, confidence interval; OS, overall survival.

($p = 0.0001$), while PS (2) has a marked but not significant effect ($p = 0.067$) (Table 4). The Kaplan-Meier curve for TTP is presented in Figure 1.

Overall Survival

Median OS was 9.9 and 9.2 months for the group younger than 70 years and ≥70 years, respectively ($p = 0.117$; Table 3 and Figure 2). The univariate and multivariate

TABLE 4. Multivariate Analysis for TTP and OS

	Hazard	95% CI	*p*
TTP			
Age, ≥70 yr vs <70 yr	1.001	0.846–1.184	0.991
PS, 2 vs 0–1	1.240	0.985–1.560	0.067
Stage, IV vs IIIB	1.314	1.128–1.530	0.0001
Histology	1.060	0.921–1.220	0.416
Adeno ca vs squamous			
Sex, female vs male	1.030	0.833–1.274	0.782
OS			
Age, ≥70 yr vs <70 yr	1.140	0.952–1.365	0.155
PS, 2 vs 0–1	1.579	1.248–1.997	0.0001
Stage, IV vs IIIB	1.653	1.397–1956	0.0001
Histology, adeno Ca vs squamous	1.086	0.935–1.261	0.281
Sex, female vs male	1.108	0.889–1.382	0.362

TTP, time to tumor progression; PS, performance status; OS, overall survival.

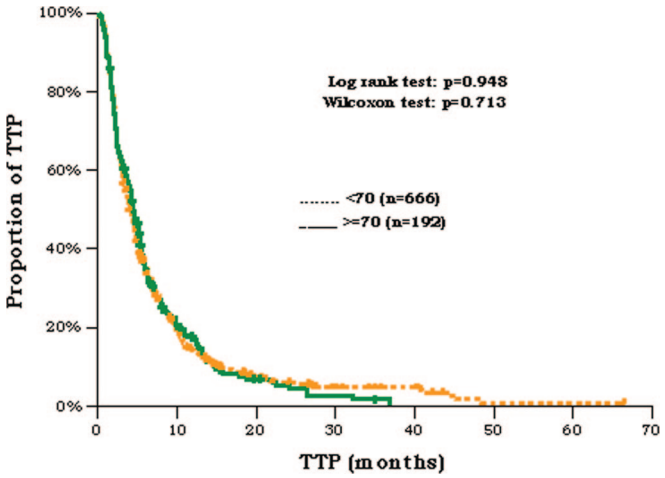

FIGURE 1. Kaplan-Meier curve for TTP, for patients <70 years and ≥70 years old. TTP, time to tumor progression.

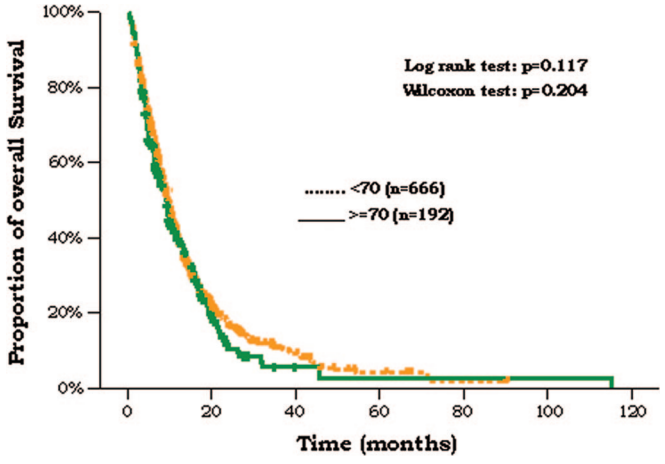

FIGURE 2. Kaplan-Meier survival curve for patients <70 years and ≥70 years old.

analysis revealed that stage of the disease ($p = 0.0001$) and performance status ($p = 0.0001$) were independents factor with significant impact on the hazard of death (Table 5).

Safety

The most frequent grade III/IV toxicity observed with the DG regimen was neutropenia, which occurred in 197 (22.9%) patients. However, there was no difference regarding the incidence of neutropenia between the two age groups ($p = 0.808$). On the contrary, the incidence of grade III/IV mucositis was significantly higher for elderly patients (0.2% versus 1.5% for patients <70 versus ≥70 years, respectively; $p = 0.011$). Similarly, there was a trend towards a higher incidence of diarrhea in elderly patients (2.1% versus 4.6% for patients aged <70 years versus ≥70 years, respectively; $p = 0.051$). No other significant difference was observed (Table 5).

DISCUSSION

Lung cancer at the elderly population is a significant public health problem. At present, about 66% of newly diagnosed NSCLC patients are older than 65 years and about one third is older than 75 years.[21] Despite this fact, until recently elderly patients were under-presented in clinical trials.[7] Furthermore, several studies have demonstrated that age is not a poor prognostic factor for OS in NSCLC.[22–24] The largest study, which included 5000 patients and evaluated the prognostic impact of 77 variables in NSCLC, yielded that age had no impact on survival, while the most important prognostic factors for survival were PS, extent of disease and weight loss in the last 6 months.[24]

Our data are in agreement with the above observations. The retrospective analysis of individual patients' data participating in six clinical trials,[10,11,16–18] yielded no significant difference in terms of response rate, TTP and OS between patients aged <70 years old, when compared with patients aged ≥70 years old; elderly patients seem to benefit from the DG regimen in a similar way like younger patients do. However, given the retrospective nature of this study, these results should be interpreted with caution.

The toxicity profile of DG regimen was also favorable in elderly patients. Indeed there was no significant difference in terms of toxicity between younger and older patients, with the exception of mucositis ($p = 0.011$) and diarrhea ($p =$

TABLE 5. Toxicity According to Age Group

	<70 (n = 666) I N	≤70 (n = 192) I N	<70 (n = 666) II N	≤70 (n = 192) II N	<70 (n = 666) III N	≤70 (n = 192) III N	<70 (n = 666) IV N	≤70 (n = 192) IV N	p^a
Neutropenia	75 (11.5)	21 (21.9)	60 (9.0)	20 (10.4)	97 (14.6)	14 (7.3)	59 (8.9)	27 (14.1)	0.808
Febrile neutropenia	6 (0.9)	2 (1.0)	7 (1.1)	1 (0.5)	11 (1.7)	1 (0.5)	243.6	7 (3.6)	0.542
Thrombo/penia	207 (31.1)	53 (27.6)	36 (5.4)	14 (7.3)	12 (1.8)	7 (3.6)	111.7	4 (2.1)	0.154
Anemia	375 (56.3)	102 (53.1)	179 (26.9)	60 (31.3)	23 (3.5)	5 (2.6)	4 (0.6)	—	0.350
Nausea/vomiting	89 (13.4)	28 (14.6)	44 (6.6)	11 (5.7)	6 (0.9)	1 (0.5)	—	2 (1.0)	0.428
Diarrhea	55 (8.3)	16 (8.3)	46 (6.9)	11 (5.7)	12 (1.8)	7 (3.6)	2 (0.3)	2 (1.0)	0.051
Mucocitis	22 (3.3)	4 (2.1)	11 (1.1)	4 (2.1)	—	2 (1.0)	1 (0.2)	1 (0.5)	0.011
Neurotoxicity	60 (9.0)	14 (7.3)	28 (4.2)	7 (3.6)	9 (1.4)	3 (1.6)	2 (0.3)	1 (0.5)	0.688
Fatigue	192 (28.8)	44 (22.9)	117 (17.6)	37 (19.3)	21 (3.2)	11 (5.7)	3 (0.5)	—	0.190

[a] Grade III/IV.

0.051). The higher incidence of mucositis and diarrhea in elderly is an expected observation; changes with age within the gastrointestinal system can result in decreased gastrointestinal motility, reduced blood flow and secretion of digestive enzymes, and mucosal atrophy, and this is a possible explanation for the higher incidence of mucositis.[25]

The optimal treatment for elderly patients with advanced NSCLC remains to be determined. A phase III multicenter trial in 191 patients (the Elderly Lung Cancer Vinorelbine Italian Study) showed that single-agent vinorelbine improved quality of life and survival compared with supportive care alone (median survival, 27 versus 21 weeks, respectively; $p = 0.04$).[13] Furthermore, a recently published randomized phase III trial, compared docetaxel (60 mg/m^2 day 1 every 3 weeks) with vinorelbine (25 mg/m^2 i.v on days 1 and 8, every 3 weeks), as first line treatment, in elderly patients with advanced NSCLC.[26] The trial enrolled 182 patients and provided significantly longer progression-free survival (5.5 months versus 3.1 month; $p = 0.001$) and ORR (22.7% versus 9.9%; $p = 0.019$) as well as a better, although not statistically significant, 1-year survival rate (58.6% versus 36.7%) in favor of docetaxel; the OS was numerically but not statistically significantly higher for the docetaxel arm when compared with the vinorelbine arm (14.3 months versus 9.9 months, respectively).

To improve the results obtained with single-agent chemotherapy in elderly patients, non-platinum-based combinations have been developed. The combination of gemcitabine/vinorelbine is the most studied regimen but the results are conflicting. Frasci et al.[14] compared the combination of vinorelbine/gemcitabine with vinorelbine alone. An interim analysis conducted on the first 120 patients demonstrated a significant benefit in favor of the combination arm, resulting in a premature trial discontinuation. Median survival time was 7 months for the combination arm and only 4.5 months for single-agent vinorelbine. This study was seriously criticized, because, single-agent vinorelbine arm outcome was similar to the outcome frequently described with supportive care alone. The subsequent Multicenter Italian Lung Cancer in the Elderly Study phase III trial compared the vinorelbine/gemcitabine combination with single-agent gemcitabine or vinorelbine.[15] This trial failed to demonstrate any benefit in favor of combination chemotherapy. For vinorelbine, gemcitabine, and the combination, median survival was 36, 28, and 30 weeks, respectively, and the probabilities of being alive at 1 year were 38%, 28%, and 30%, respectively.[15]

Although, cisplatin-based doublets are considered as the standard treatment in advanced NSCLC,[27] no prospective randomized phase III data support this fact in elderly population. However, retrospective data from many investigators support that elderly patients experienced more profound myelotoxicity and had greater risk of chemotherapy-related death from cisplatin administration than younger patients.[28,29]

Evaluating the different treatment options for elderly patients with NSCLC, it is very important to effectively select these patients who are suitable for chemotherapy. A comprehensive geriatric assessment should always be done, with the use of validated instruments. This will allow the clinical oncologist to evaluate functional status, comorbidities, socioeconomic status, nutritional status, polypharmacy, and the presence of geriatric syndromes.[30] This approach will allow the identification of potentially treatable problems (such as depression or malnutrition) that may otherwise decrease tolerability and increase toxicity and consequently to compromise the outcome. In summary, this retrospective analysis of pooled data clearly demonstrates that the combination of docetaxel and gemcitabine is an active and well-tolerated regimen for elderly patients with advanced/metastatic NSCLC. Although in a previous study we demonstrated that the DG regimen is superior to docetaxel monotherapy in the general population[17] this remains to be specifically proved in elderly patients in the context of a prospective randomized trial.

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