VOLUME 36 · NUMBER 25 · SEPTEMBER 1, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials

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Published at jco.org on July 20, 2018.

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Clinical trial information: NCT01405586, NCT01656551.

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0732-183X/18/3625w-2585w/$20.00

ABSTRACT

Purpose
To test the efficacy of adding cisplatin to first-line treatment for elderly patients with advanced non–small-cell lung cancer (NSCLC) within a combined analysis of two parallel phase III trials, MILES-3 and MILES-4.

Patients and Methods
Patients with advanced NSCLC who were older than age 70 years with Eastern Cooperative Oncology Group performance status 0 to 1 were randomly assigned to gemcitabine or pemetrexed, without or with cisplatin. In each trial, 382 events were required to detect a hazard ratio (HR) of death of 0.75, with 80% power and two-tailed α of .05. Trials were closed prematurely because of slow accrual, but the joint database allowed us to analyze the efficacy of cisplatin on the basis of intention-to-treat and adjusted by trial, histotype, non-platinum companion drug, stage, performance status, sex, age, and size of the study center.

Results
From March 2011 to August 2016, 531 patients (MILES-3, 299; MILES-4, 232) were assigned to gemcitabine or pemetrexed without (n = 268) or with cisplatin (n = 263). Median age was 75 years, 79% were male, and 70% had nonsquamous histology. At a median 2-year follow-up, 384 deaths and 448 progression-free survival events were recorded. Overall survival was not significantly prolonged with cisplatin (HR, 0.86; 95% CI, 0.70 to 1.05; $P = .14$) and global health status score of quality of life was not improved, whereas progression-free survival (HR, 0.76; 95% CI, 0.63 to 0.92; $P = .005$) and objective response rate (15.5% *v* 8.5%; $P = .02$) were significantly better. Significantly more severe hematologic toxicity, fatigue, and anorexia were found with cisplatin.

Conclusion
The addition of cisplatin to single-agent chemotherapy does not significantly prolong overall survival, and it does not improve global health status score of quality of life in elderly patients with advanced NSCLC.

J Clin Oncol 36:2585-2592. © 2018 by American Society of Clinical Oncology

ASSOCIATED CONTENT

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DOI: https://doi.org/10.1200/JCO.2017.76.8390

Data Supplement
DOI: https://doi.org/10.1200/JCO.2017.76.8390

DOI: https://doi.org/10.1200/JCO.2017.76.8390

INTRODUCTION

Non–small-cell lung cancer (NSCLC) is the most common cancer in the world and the leading cause of cancer deaths in Western countries.[1] More than one third of lung cancer cases are diagnosed in patients older than age 70 years, and the majority of elderly patients have metastatic disease at the time of diagnosis.[2] In these cases, a palliative treatment with single-agent gemcitabine or vinorelbine has long been considered the standard therapy on the basis of the results of ELVIS (Elderly Lung Cancer Vinorelbine Italian Study) and MILES (Multicenter Italian Lung Cancer in the Elderly Study) trials.[3-6] In 2011, Quoix et al[7] compared the combination of once-per-month carboplatin and once-per-week paclitaxel versus single-agent gemcitabine or vinorelbine as first-line treatment for elderly patients with advanced NSCLC. The combination improved overall survival (OS) at the cost of higher

toxicity (deaths as a result of toxicity were 4.4% *v* 1.3% in the two arms). Safety concerns negatively affected the use of this combination in clinical practice, notwithstanding the positive result.

Even in the era of precision medicine, excluding 15% to 20% of patients with an epidermal growth factor receptor (EGFR)–mutated or anaplastic lymphoma kinase (ALK)–positive tumor and another 25% to 30% with a programmed death-ligand 1(PD-L1)–positive tumor, a combination chemotherapy that includes cisplatin remains the standard treatment for the majority of adult patients with advanced NSCLC. However, there are concerns about the tolerability and feasibility of using cisplatin for elderly patients who might have an increased risk of life-threatening toxicity.[8-10] In two phase I/II studies (MILES-2P [Cisplatin Plus Gemcitabine or Vinorelbine for Elderly Patients With Advanced Non–Small-Cell Lung Cancer]), we found that the combination of cisplatin at 60 mg/m^2 with gemcitabine was feasible and worthy of a further phase III comparison.[11]

On these bases, we designed two randomized clinical trials, MILES-3 (Cisplatin in Combination With Gemcitabine for Elderly Patients With Lung Cancer) and MILES-4 (A Factorial Study of Cisplatin Added to Pemetrexed or Gemcitabine in Elderly Patients With Nonsquamous Lung Cancer), to test whether the addition of cisplatin to single-agent chemotherapy prolongs survival of elderly patients with advanced NSCLC who do not have an EGFR mutation.[12] In the two-arm MILES-3 trial, the combination of cisplatin and gemcitabine was compared with gemcitabine alone in patients with any tumor histology. The ensuing four-arm MILES-4 trial compared gemcitabine or pemetrexed with gemcitabine plus cisplatin or pemetrexed plus cisplatin in patients with nonsquamous histology, based on the hypothesis that pemetrexed might be more effective and less toxic than gemcitabine for patients with nonsquamous histology.[13] Both trials were closed prematurely because of slow accrual, but a joint analysis allowed the researchers to properly address the main question of the addition of cisplatin according to the advice from the Independent Data Monitoring Committee.

PATIENTS AND METHODS

Eligibility Criteria

Eligible patients had previously untreated advanced NSCLC with any (MILES-3) or nonsquamous (MILES-4) histology, measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, age 70 years or older, Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, life expectancy $>$ 3 months, and adequate organ function, and they provided signed informed consent.

Key exclusion criteria were the presence of any unstable systemic disease or medical contraindication to the study medications, other malignancies within 5 years (except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer or surgically resected prostate cancer with normal prostate-specific antigen, symptomatic brain metastasis, or spinal cord compression not yet treated with surgery and/or radiation. Patients with activating EGFR mutations were excluded. The protocols were approved by institutional ethical committees at each participating center.

Treatment and Trial Procedures

MILES-3 and MILES-4 were open-label, multicenter, randomized phase III studies. In MILES-3, patients were randomly assigned in a 1:1 ratio to receive gemcitabine 1,200 mg/m^2 intravenously on days 1 and 8 once every 3 weeks for six cycles (standard arm) or cisplatin 60 mg/m^2 intravenously on day 1 plus gemcitabine 1,000 mg/m^2 intravenously on days 1 and 8 once every 3 weeks for six cycles (experimental arm).

MILES-4 had a factorial design and patients were randomly assigned in a 1:1:1:1 ratio to one of four treatment arms. Patients in arm A received gemcitabine 1,200 mg/m^2 alone on days 1 and 8 once every 3 weeks for six cycles, arm B received gemcitabine 1,000 mg/m^2 on days 1 and 8 plus cisplatin 60 mg/m^2 on day 1 once every 3 weeks for six cycles, arm C received pemetrexed 500 mg/m^2 alone on day 1 once every 3 weeks for six cycles, and arm D received pemetrexed 500 mg/m^2 plus cisplatin 60 mg/m^2 on day 1 once every 3 weeks for six cycles. All the patients received oral folic acid 400 mg once per day plus an injection of vitamin B_{12} 1,000 mg once every 9 weeks beginning 1 to 2 weeks before the first dose of chemotherapy and continuing until 3 weeks after the last dose, and dexamethasone 4 mg twice per day for 3 days beginning on the day before chemotherapy until the day after chemotherapy.

Dose reductions and delays of chemotherapy as a result of toxicity were applied as in clinical practice. The use of granulocyte colony-stimulating factors was allowed as secondary prophylaxis in the case of grade 4 neutropenia. Activities of daily living (ADL) and instrumental ADL (IADL) scales were assessed at baseline.

Random assignments were performed centrally at the Clinical Trials Unit of the National Cancer Institute of Naples via a Web-based minimization procedure. In MILES-3, random assignments were stratified by center, performance status (0 *v* 1), tumor stage (IIIB *v* IV), and histotype (squamous *v* nonsquamous). In MILES-4 strata were center, performance status (0 *v* 1), tumor stage (IIIB *v* IV), and sex.

Outcomes

OS, defined as the time between the date of random assignment and the date of death, was the primary end point in both studies. Secondary end points in both studies included progression-free survival (PFS), objective response rate (ORR), toxicity, and quality of life (QOL). PFS was defined as the time between the date of random assignment and the date of disease progression or death, whichever occurred first. Patients who did not progress were censored on the date of the last follow-up visit.

Response was assessed by investigators according to RECIST v1.1. Patients not evaluated because of death or toxicity or refusal of treatment or loss to follow-up before the first restaging were considered nonresponders. Adverse events were coded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, and toxicity was described as the worst grade suffered for each item by each patient at any time during the treatment. Global health status score of QOL was calculated at each time point by deriving the mean raw score of items 29 and 30 of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) questionnaire and linearly transforming it into a scale ranging from 0 to 100 in which higher values represent better function.[14] QOL response was calculated by using a 10-point threshold, previously defined as being clinically relevant.[15]

Statistical Analysis

The sample size in both trials was based on the primary outcome, the effect on survival of the addition of cisplatin to single-agent treatment. Both studies had an 80% power to detect a hazard ratio (HR) of death of 0.75 in favor of the combination arm. With a two-tailed alpha error of .05, 381 events were required in MILES-3 and 382 events were required in MILES-4. Planned sample size was 480 patients for MILES-3 and 550 for MILES-4 (EAST 3.1; Cytel Software, Cambridge, MA). MILES-4 also planned a second superiority comparison to assess the effect on survival of pemetrexed compared with gemcitabine. This analysis will be reported separately.

Joint efficacy and safety analyses were performed according to the intention-to-treat strategy. The analyses were performed when all the

patients in both studies had completed study treatment and the planned number of events for primary analysis was reached by adding together the events reported in the two studies. No adjustment was planned for multiple comparison. All the statistical tests were interpreted as significant with a *P* value of less than 5%.

Median follow-up was calculated according to the Schemper's reverse Kaplan-Meier technique.[16] Survival curves were described according to the Kaplan-Meier product-limit method.[17] HR was estimated by using a stratified Cox proportional hazards model adjusted by size of center (according to tertiles of the number of enrolled patients), sex, age, PS (0 *v* 1), and tumor stage (IIIB *v* IV). Four strata were defined for the analysis according to study (MILES-3 or MILES-4): histotype (squamous or nonsquamous) and companion drug (gemcitabine or pemetrexed). A secondary analysis further introduced baseline data from geriatric ADL and IADL scales into the Cox proportional hazards model as a result of our previous findings on the significant prognostic effect of such measures in the MILES study.[18]

First-order interactions between treatment and the main prognostic and potentially confounding variables were tested by likelihood ratio test of two nested models with and without interaction; the effects of treatments were reported as HRs and 95% CIs for subgroup categories in a Forest plot.

Patients with at least one target or nontarget lesion at baseline according to RECIST v1.1 were eligible for response assessment. ORRs (complete plus partial) in the two arms were compared by stratified Mantel-Haenszel test, adjusted by size of center, sex, age, PS, and tumor stage and were stratified by study, histotype, and companion drug. Patients who received at least one dose of the study drug were eligible for safety assessment. All toxicity grades and severe (grade $>$ 2) toxicities were compared between the two arms by stratified Mantel-Haenszel test.

Mean change from baseline in global health status score of QOL at each time point was compared between the two arms in a linear regression model, adjusted by the previous covariates and the baseline global health status score of QOL. QOL response was compared with χ^2 test. Statistical analyses were performed using STATA MP 14.1 software (STATA, College Station, TX).

RESULTS

Patient Characteristics

Between March 31, 2011, and August 5, 2016, a total of 531 patients were enrolled in the two studies (299 in MILES-3 and 232 in MILES-4) in 46 Italian centers. Overall, 268 patients were assigned to receive monotherapy with gemcitabine or pemetrexed, and 263 were assigned to receive combination chemotherapy with gemcitabine or pemetrexed plus cisplatin (Fig 1). All patients were included in the survival analyses. Baseline characteristics of the patients were balanced between the arms (Table 1). Comorbidities were similarly distributed between the arms: more than half the patients had hypertension, and almost 30% had chronic obstructive pulmonary disease (Appendix Table A1, online only). Three patients in the monotherapy arm and six patients in the combination arm withdrew consent after random assignment and never started treatment. Three patients in the monotherapy arm and six patients in the combination arm died before starting

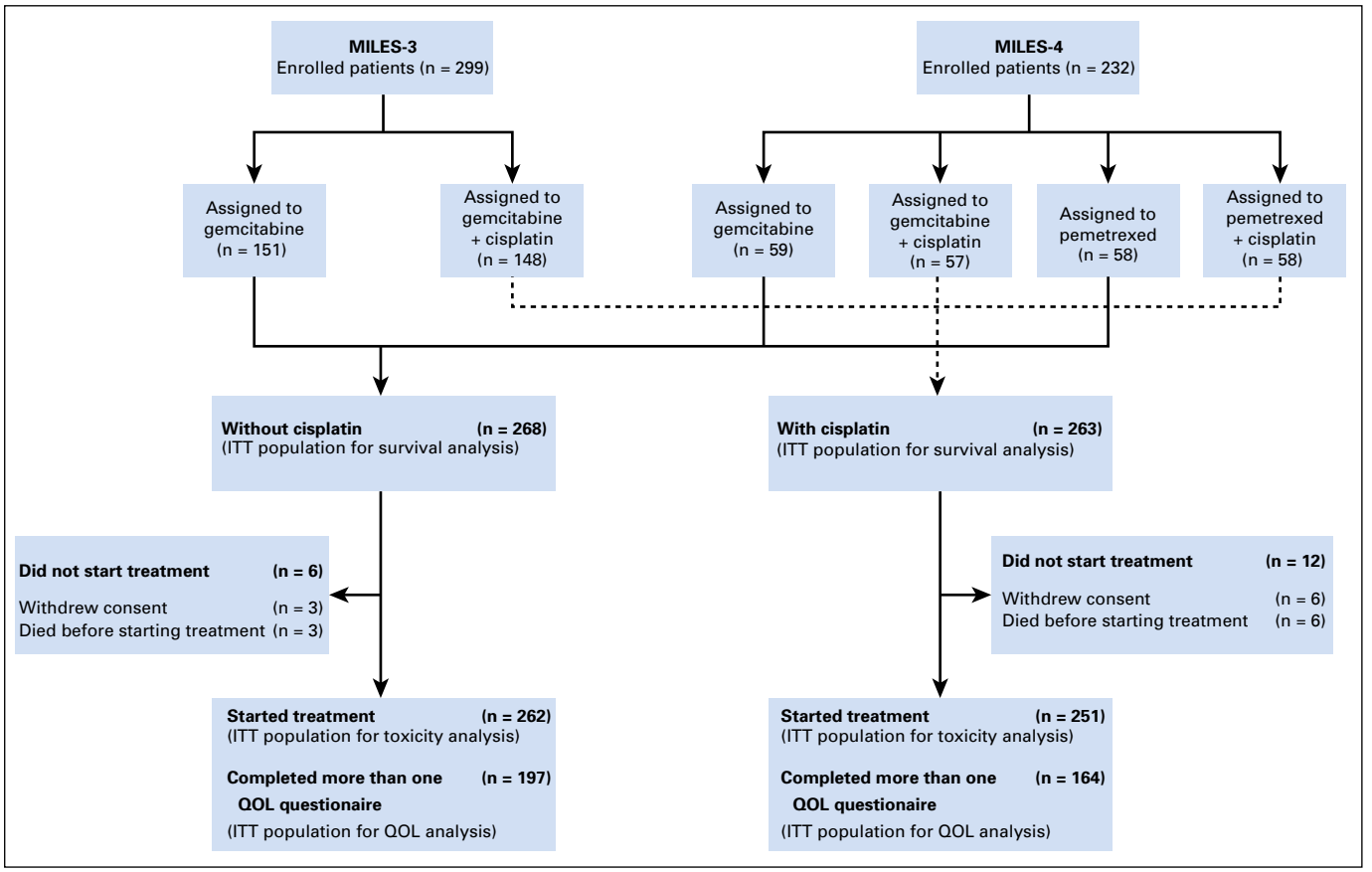

Fig 1. CONSORT diagram. ITT, intention to treat; MILES-3, Cisplatin in Combination With Gemcitabine for Elderly Patients With Lung Cancer; MILES-4, A Factorial Study of Cisplatin Added to Pemetrexed or Gemcitabine in Elderly Patients With Nonsquamous Lung Cancer; QOL, quality of life.

Table 1. Distribution of Patients' Baseline Characteristics by Treatment Arm

Characteristic	Without Cisplatin (n = 268)		With Cisplatin (n = 263)	
	No.	%	No.	%
Age, years				
< 75	131	48.9	139	52.8
75-80	108	40.3	101	38.4
≥ 80	29	10.8	23	8.7
Sex				
Male	215	80.2	203	77.2
Female	53	19.8	60	22.8
Performance status				
0	114	42.5	116	44.1
1	154	57.5	147	55.9
Histotype				
Squamous	79	29.5	78	29.7
Nonsquamous	189	70.5	185	70.3
Stage				
IIIB	20	7.5	16	6.1
IV	248	92.5	247	93.9
Smoking habit				
Current smokers	73	27.2	66	25.1
Former smokers	159	59.3	160	60.8
Never Smokers	36	13.4	34	12.9
Unknown	0		3	1.1
ADL score				
6	202	75.4	200	76.1
< 6	26	9.7	24	9.1
Unknown	40	14.9	39	14.8
Percent of IADL independency				
100	84	31.3	76	28.9
99-75	52	19.4	62	23.6
74-50	67	25.0	61	23.2
49-25	24	9.0	22	8.4
< 25	1	0.4	1	0.4
Unknown	40	14.9	41	15.6
Companion drug				
Gemcitabine	210	78.3	205	77.9
Pemetrexed	58	21.6	58	22.1

Abbreviations: ADL, activities of daily living; IADL, instrumental ADL.

treatment. Therefore, 262 and 251 patients, respectively, were included in the compliance and safety analyses.

Treatment Compliance

The majority of patients received gemcitabine as monotherapy (78.3%) or associated with cisplatin (77.9%). The median number of treatment cycles was three (interquartile range, three to six) without cisplatin and four (interquartile range, two to six) with cisplatin. Overall, 89 patients (34.0%) treated without cisplatin and 102 patients (40.6%) treated with cisplatin completed the planned treatment. Sixteen patients (6.1%) treated without cisplatin and 30 patients (11.7%) treated with cisplatin stopped treatment as a result of toxicity or refusal of treatment (Appendix Table A2, online only). Information on second-line treatment after disease progression was reported in 186 patients (35.0%) with no differences between treatment arms (Appendix Table A3, online only)

Primary Analysis

Data from the two studies were locked and combined on November 22, 2016, with a median follow-up of 24 months. Overall, 384 deaths were recorded (200 in the monotherapy arm and 184 in the combination arm). HR was 0.86 (95% CI, 0.70 to 1.05; $P = .14$), and median OS was 7.5 months (95% CI, 6.2 to 9.5 months) in the monotherapy arm and 9.6 months (95% CI, 8.1 to 11.7 months) in the combination arm (Fig 2A). Similar results (HR 0.96; 95% CI, 0.74 to 1.15; $P = .48$) were observed when ADL and IADL scores were added to the model (447 patients and 328 deaths were available). No statistically significant interaction was found between treatment effect (HR of death) and the main prognostic and potentially confounding variables (Fig 3).

Secondary Analyses

For PFS analyses, the total number of events was 448: 232 in the monotherapy arm and 216 in the combination arm. HR was 0.76 (95% CI, 0.63 to 0.92; $P = .006$), and median PFS was 3.0 months (95% CI, 2.5 to 3.8 months) in the monotherapy arm and 4.6 months (95% CI, 4.1 to 5.3 months) in the combination arm (Fig 2B). In addition, the analysis accounting for ADL and IADL scores as covariates produced similar results (HR, 0.78; 95% CI, 0.63 to 0.96; $P = .02$).

According to RECIST v1.1, 22 of 260 eligible patients achieved an ORR of 8.5% (95% CI, 5.4% to 12.5%) in the monotherapy arm, and 38 of 246 achieved an ORR of 15.5% (95% CI, 11.2 to 20.6) in the combination arm ($P = .02$; Appendix Table A4, online only).

Patients receiving the cisplatin combination experienced significantly more hematologic and neurologic toxicity, mucositis, nausea, and vomiting and significantly more severe thrombocytopenia, leucopenia, neutropenia, febrile neutropenia, fatigue, and anorexia (see Appendix Tables 2 and A5 [online only] for complete information). Significantly more fever and an increase in ALT and AST were reported with monotherapy. There were three (1.1%) deaths as a result of toxicity with monotherapy and 2 (0.7%) with the cisplatin combination.

Global health status score of QOL after cycles 1 and 2 was not improved in patients receiving cisplatin (Fig 4). Improvement of at least 10 points in QOL was reported in 77 (39.3%) of 197 patients without cisplatin and 61 (37.2%) of 164 patients with cisplatin ($P = .80$).

DISCUSSION

The joint analysis of MILES-3 and MILES-4 trials shows that the addition of cisplatin to single-agent chemotherapy for elderly patients with advanced NSCLC does not significantly prolong OS and does not improve global health status score of QOL. Therefore, combination chemotherapy that includes cisplatin should no longer be proposed in this clinical setting.

This study has several strengths that increase the generalizability of its findings. First, it is the largest trial devoted to test the addition of a platinum compound to single-agent chemotherapy in elderly patients with NSCLC. Second, drugs used in the control arm are recognized worldwide as standard treatments. Third, the experimental platinum-based combination was properly selected through the phase II MILES-2P studies. In those trials, 60 mg/m^2 of cisplatin could be added to gemcitabine but only 40 mg/m^2 could be added to vinorelbine,

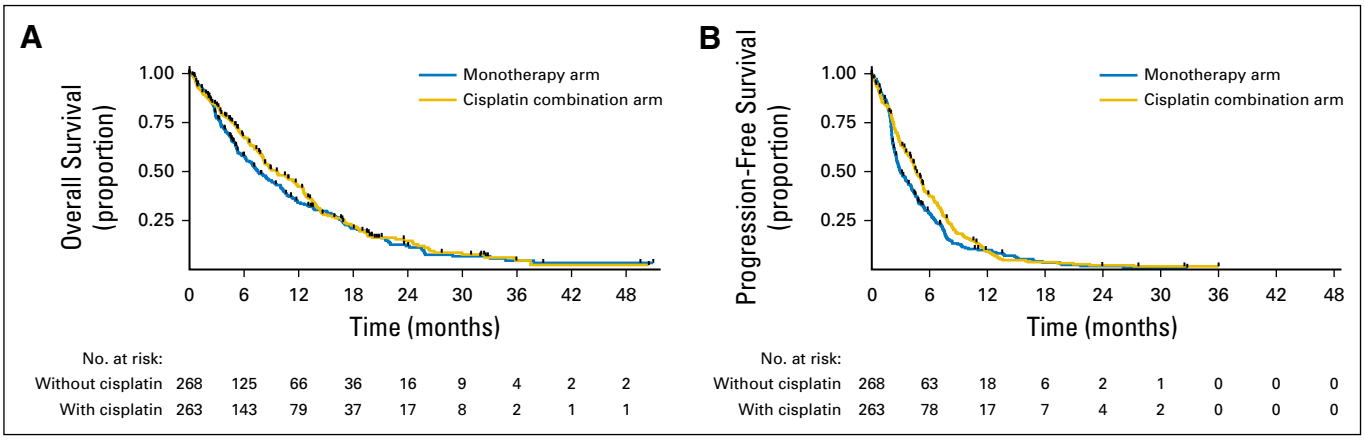

Fig 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival. Black vertical lines represent censoring.

and the combination with the higher dose of cisplatin was selected for further study.[11] Fourth, the design of MILES-4 allowed for the introduction of pemetrexed in this factorial study to manage patients with nonsquamous histology, once it became clear that the drug was being prescribed more often in this subgroup of patients. Fifth, there is a high level of internal consistency among results in the different outcomes, with statistically significant but clinically poor improvements in PFS and ORR; such small advantages are transient and do not significantly change the OS rate. Such results are homogeneous across all subgroups.

Few prospective phase III randomized trials have tested the effect of the addition of a platinum compound to single-agent chemotherapy as first-line treatment of patients with NSCLC who are older than age 70 years. The Intergroup Trial JCOG0803/WJOG4307L (Randomized Phase III Trial Comparing Weekly Docetaxel Plus Cisplatin Versus Docetaxel Monotherapy Every 3 Weeks in Elderly Patients With Advanced Non–Small-Cell Lung Cancer) compared a dose of a combination of cisplatin and docetaxel once per week to a dose of docetaxel once every 3 weeks. The trial was interrupted early (with 276 enrolled patients of the 380 planned), because it was clear at the first interim analysis that

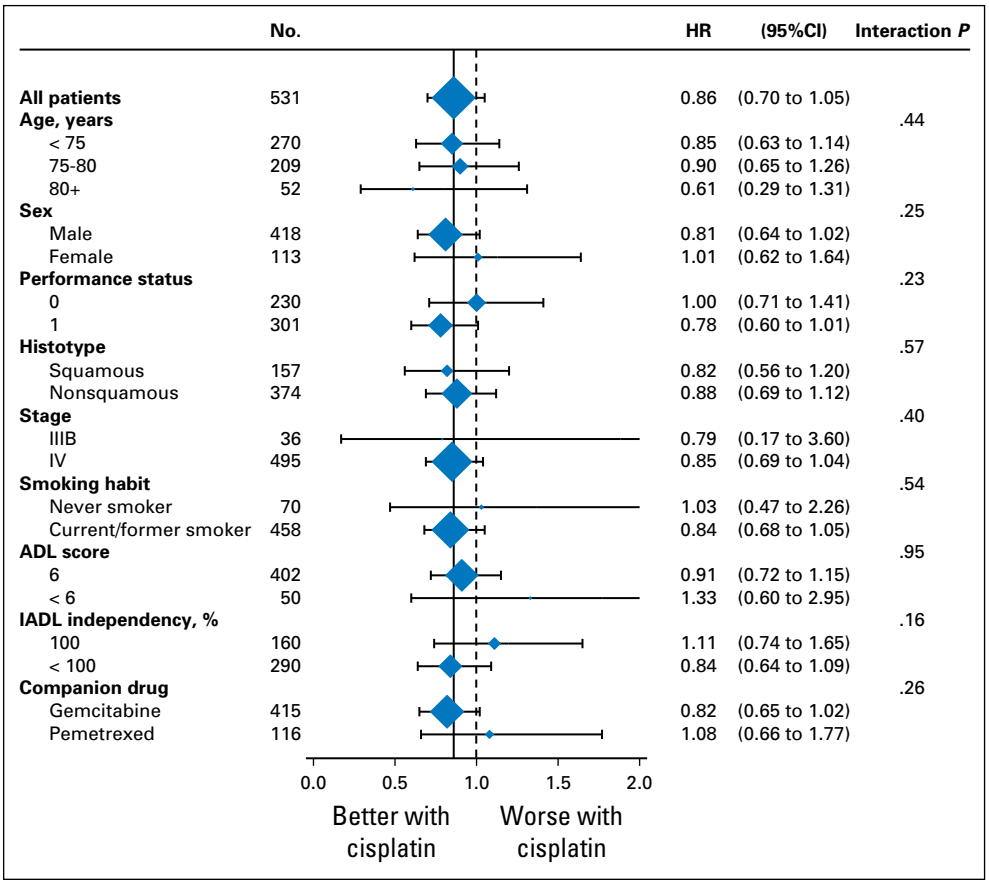

Fig 3. Subgroup analysis. First-order interactions between treatment and main prognostic and potentially confounding variables tested by likelihood ratio test. ADL, activities of daily living; HR, hazard ratio; IADL, instrumental ADL.

Table 2. Any Grade and Severe Toxicity Recorded in > 5% of Patients by Treatment Arm (CTCAE 4.0)

	Any Grade					Grade > 2				
	Without Cisplatin		With Cisplatin			Without Cisplatin		With Cisplatin		
Toxicity	No.	%	No.	%	*P**	No.	%	No.	%	*P**
Anemia	86	34.0	131	54.8	<.001	9	3.6	14	5.9	.22
Leucopenia	30	11.9	47	19.7	.02	3	1.2	15	6.3	.002
Neutropenia	36	14.2	61	25.5	.001	11	4.3	29	12.1	.001
Febrile neutropenia	2	0.8	16	6.7	<.001	2	0.8	16	6.7	<.001
Piastrinopenia	33	13.0	64	26.8	<.001	7	2.8	17	7.1	.03
Cardiac disorders	8	3.2	16	6.7	.07	2	0.8	3	1.3	.60
Cough	11	4.3	14	5.9	.41	0	0.0	1	0.4	.30
Dyspnea	32	12.6	20	8.4	.13	7	2.8	10	4.2	.40
Fatigue	132	52.2	145	60.7	.06	17	6.7	36	15.1	.003
Weight loss	13	5.1	20	8.4	.15	0	0.0	1	0.4	.30
Anorexia	42	16.6	41	17.2	.85	2	0.8	8	3.3	.04
Fever	61	24.1	33	13.8	.003	0	0.0	0	0.0	—
Pain	15	5.9	16	6.7	.69	5	2.0	3	1.3	.54
Constipation	48	19.0	48	20.1	.72	3	1.2	4	1.7	.66
Diarrhea	21	8.3	21	8.8	.84	2	0.8	3	1.3	.60
Mucositis	29	11.5	45	18.8	.02	2	0.8	7	2.9	.08
Nausea	57	22.5	78	32.6	.01	1	0.4	2	0.8	.52
Stomach pain	8	3.2	15	6.3	.09	0	0.0	1	0.4	.30
Vomiting	20	7.9	49	20.5	<.001	1	0.4	4	1.7	.17
ALT	29	11.5	8	3.3	<.001	6	2.4	1	0.4	.07
AST	29	11.5	6	2.5	<.001	5	2.0	1	0.4	.12
Creatinine	14	5.5	23	9.6	.08	2	0.8	2	0.8	.96
Hyperglycemia	16	6.3	14	5.9	.84	0	0.0	3	1.3	.08
Paresthesia	7	2.8	16	6.7	.04	0	0.0	1	0.4	.29
Skin disorders	13	5.1	13	5.4	.86	1	0.4	1	0.4	.98

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.
**P* value from stratified Mantel-Haenszel test.

the probability that the combination would significantly prolong survival was < 1%.[19]

The French IFCT-0501 (Carboplatin and Weekly Paclitaxel Doublet Chemotherapy in Elderly Patients With Non–Small-Cell Lung Cancer [NSCLC]) trial enrolled 451 patients and compared a combination of carboplatin (area under the curve of 6 every 4 weeks) and paclitaxel (90 mg/m^2 on days 1, 8, and 15) once every 4 weeks versus standard vinorelbine or gemcitabine. The experimental treatment was significantly more toxic, particularly for neutropenia and asthenia, with a 4.4% incidence of death as a result of toxicity (compared with 1.3% in the control arm). This was probably a result of the high drug doses in the combination arm and of including patients with adverse clinical conditions (PS 2) in the trial. Nevertheless, there was a statistically significant prolongation of OS (median, 6.2 *v* 10.3 months; HR, 0.64) and PFS and an improvement in response rate, although there was no difference in global health status score of QOL.[7] MILES-3 and MILES-4 results are consistent with Japanese negative data on the addition of cisplatin to single-agent chemotherapy, and they actually represent the first evidence coming from a trial with a control arm that was considered a standard worldwide. Acknowledging the limitations of indirect comparisons, it seems that the addition of carboplatin yielded better results than the addition of cisplatin, although the evidence comes from only one trial, the IFCT-0501, in which toxicity was relevant; caution is required when generalizing these results to clinical practice.

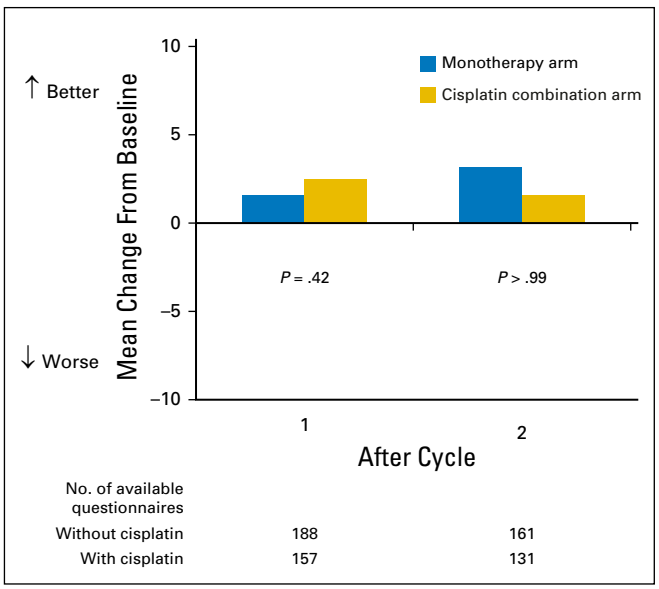

Fig 4. Mean change from baseline of the global health status score of quality of life after cycles 1 and 2.

The major weakness of the MILES-3 and MILES-4 studies derives from the slow enrollment and the need to join the two trials to reach the sample size required to assess the efficacy of cisplatin. We managed this issue using stratification by all the constitutive differences in inclusion criteria and treatment plan between the

two trials. In addition, the two trials were conducted during the same timeframe, by the same cooperative group, with similar protocol rules, the same coordination unit, and the same data management system, suggesting that heterogeneity in the conduct of the two studies is limited and might not have any effect on the final result.

Thanks to the availability of new drugs targeting immune checkpoints and molecular alterations, it might seem that optimization of chemotherapy is no longer an important issue. However, according to the currently available drugs for patients with advanced NSCLC, those eligible for treatment with tyrosine kinase inhibitors represent a small proportion of patients because of the relative rarity of EGFR, ALK, and the molecular defects of reactive oxygen species. Conversely, immunotherapy is available as a single drug in first-line therapy for patients selected on the basis of PD-L1 expression, and its use as second-line therapy, independent of PD-L1 expression, is planned after chemotherapy. Antiangiogenic drugs are always used in combination with chemotherapy. Overall, we estimate that approximately 80% of patients with advanced NSCLC still receive chemotherapy during their lifetime: approximately 60% as first-line and 40% as second-line treatment. Therefore, we believe that refining chemotherapy, particularly for the elderly population, in which its toxicity may actually prevent the use of more recent and innovative treatment options in some cases, is important.

In conclusion, the addition of cisplatin to single-agent chemotherapy does not significantly prolong OS nor does it improve global health status score of QOL of elderly patients with advanced NSCLC. It should no longer be among the preferred options for first-line treatment in clinical practice. This result fully supports the treatment algorithm proposed for elderly patients in the European Society of Medical Oncology guidelines.[20] Standard treatment should remain single-agent chemotherapy whereas carboplatin-based combinations might be considered as an alternative in selected cases, with caution regarding potential toxicity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Support

Partially supported by Grant No. FARM8KAJZK from the Italian Drug Agency and by Eli Lilly.

Prior Presentation

Results were presented at the 53rd Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 2-6, 2017.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Cisplatin-Based First-Line Treatment of Elderly Patients With Advanced Non–Small-Cell Lung Cancer: Joint Analysis of MILES-3 and MILES-4 Phase III Trials

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Acknowledgment

This study combined two academic nonprofit trials. The National Cancer Institute of Naples sponsored both trials and was responsible for designing the study, performing the trials, collecting and analyzing the data, writing the report, and making the decision to submit the report for publication.

MILES-3 was partially supported by the Italian Drug Agency (AIFA) Grant No. ARM8KAJZK. Eli Lilly provided the pemetrexed, free of charge, and provided partial funding for the MILES-4 study.

M.C.P., S.S., G.D., C. Gallo, and F.P. had access to the raw data.

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The trials were available in public registries with the following codes: MILES-3: ClinicalTrials.gov NCT01405586, EudraCT No. 2009-013540-36; MILES-4: ClinicalTrials.gov NCT01656551, EudraCT No. 2012-000164-25.

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Table A1. Distribution of Comorbidities at Baseline

Comorbidity	Without Cisplatin (n = 268)		With Cisplatin (n = 263)	
	No.	%	No.	%
Hypertension	161	60.1	155	58.9
Peripheral vascular disorders	29	10.8	26	9.9
Arrhythmia	28	10.5	26	9.9
Acute coronary syndrome	21	7.8	21	8.0
Central vascular disorders	19	7.1	15	5.7
Heart failure	2	0.7	2	0.8
Other cardiovascular	27	10.1	15	5.7
Chronic obstructive pulmonary disease	84	31.3	77	29.3
Other pulmonary disease	18	6.7	10	3.8
Chronic liver disease	45	16.8	59	22.4
Gastritis	15	5.6	7	2.7
Gastric/duodenal ulcer	7	2.6	6	2.3
Cholelithiasis	7	2.6	7	2.7
Other GI disease	16	6.0	25	9.5
Diabetes	45	16.8	59	22.4
Endocrine/metabolic disorders	34	12.7	29	11.3
Prostatic hypertrophy	52	19.4	45	17.1
Chronic renal failure	7	2.6	2	0.8
Renal calculi	2	0.7	5	1.9
Urinary incontinence	0		2	0.8
Other genitourinary disease	10	3.7	6	2.3
Arthrosis	18	6.7	16	6.1
Connective tissue disorders	4	1.5	7	2.7
Osteoporosis	8	3.0	8	3.0
Other musculoskeletal disease	9	3.4	14	5.3
Depression	9	3.4	8	3.0
Dementia	2	0.7	1	0.4
Parkinsonism	1	0.4	1	0.4
Other neurologic disease	9	3.4	5	1.9
Skin disorders	3	1.1	5	1.9
Hematologic disorders	5	1.9	4	1.5
Other previous cancer	19	7.1	11	4.2
Other comorbidity	12	4.5	14	5.3

Table A2. Treatment Compliance

Compliance	Without Cisplatin (n = 262)		With Cisplatin (n = 251)	
	No.	%	No.	%
Median No. of cycles (interquartile range)	3 (3-6)		4 (2-6)	
Cause of treatment interruption				
Completion	89	34.0	102	40.6
Progression or death	138	52.7	96	38.2
Toxicity	11	4.2	17	6.8
Refusal of treatment	5	1.9	13	5.2
Comorbidity	1	0.4	3	1.2
Protocol violation	2	0.8	1	0.4
Logistical problem	3	1.1	2	0.8
Unknown	13	5.0	17	6.8

Table A3. Distribution of Second-Line Treatments by Treatment Arm

Treatment	Without Cisplatin	With Cisplatin	Total
EGFR TKI	29	35	64
Docetaxel	18	28	46
Vinorelbine	19	3	22
Pemetrexed	10	6	16
Platinum-based chemotherapy	9	4	13
Nivolumab	5	7	12
Gemcitabine	3	5	8
ALK TKI	1	4	5
Total	94	92	186

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Table A4. Objective Response Rate by Treatment Arm

	Without Cisplatin (n = 260)			With Cisplatin (n = 246)			
Response	No.	%	95% CI	No.	%	95% CI	*P**
Responders	22	8.5	5.4 to 12.5	38	15.5	11.2 to 20.6	.02
CR	1	0.4		0			
PR	21	8.1		38	15.5		
Nonresponders							
SD	63	24.2		61	24.8		
PD	175	65.3		147	55.9		

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.
**P* value from stratified Mantel-Haenszel test.

Table A5. Any Grade and Severe Toxicity According to CTCAE Categories and Subcategories by Treatment Arm

	Any Grade					Grade > 2				
	Without Cisplatin		With Cisplatin			Without Cisplatin		With Cisplatin		
Toxicity Category	No.	%	No.	%	*P**	No.	%	No.	%	*P**
Blood	88	34.8	137	57.3	< .001	13	5.1	33	13.8	< .001
Anemia	86	34.0	131	54.8	< .001	9	3.6	14	5.9	.22
Febrile neutropenia	2	0.8	16	6.7	< .001	2	0.8	16	6.7	< .001
Cardiac	8	3.2	16	6.7	.07	2	0.8	3	1.3	.60
Ear	2	0.8	3	1.3	.62	0	0.0	0	0.0	—
Eye	3	1.2	3	1.3	.92	0	0.0	0	0.0	—
Endocrine	1	0.4	0	0.0	.34	0	0.0	0	0.0	—
General	162	64.0	155	64.9	.85	23	9.1	38	15.9	.02
Fatigue	132	52.2	145	60.7	.06	17	6.7	36	15.1	.003
Fever	61	24.1	33	13.8	.003	0	0.0	0	0.0	—
Pain	15	5.9	16	6.7	.69	5	2.0	3	1.3	.54
Hepatobiliary	0	0.0	1	0.4	.29	0	0.0	1	0.4	.29
Immune system	1	0.4	4	1.7	.16	0	0.0	0	0.0	—
Infection	7	2.8	5	2.1	.61	1	0.4	3	1.3	.30
GI	111	43.9	122	51.0	.10	9	3.6	17	7.1	.08
Constipation	48	19.0	48	20.1	.72	3	1.2	4	1.7	.66
Diarrhea	21	8.3	21	8.8	.84	2	0.8	3	1.3	.60
Mucositis	29	11.5	45	18.8	.02	2	0.8	7	2.9	.08
Nausea	57	22.5	78	32.6	.01	1	0.4	2	0.8	.52
Stomach pain	8	3.2	15	6.3	.09	0	0.0	1	0.4	.30
Vomiting	20	7.9	49	20.5	< .001	1	0.4	4	1.7	.17
Investigations	108	42.7	138	57.7	< .001	23	9.1	49	20.5	< .001
ALT	29	11.5	8	3.3	< .001	6	2.4	1	0.4	.07
AST	29	11.5	6	2.5	< .001	5	2.0	1	0.4	.12
Creatinine	14	5.5	23	9.6	.08	2	0.8	2	0.8	.96
Neutropenia	36	14.2	61	25.5	.001	11	4.3	29	12.1	.001
Leucopenia	30	11.9	47	19.7	.02	3	1.2	15	6.3	.002
Piastrinopenia	33	13.0	64	26.8	< .001	7	2.8	17	7.1	.03
Weight loss	13	5.1	20	8.4	.15	0	0.0	1	0.4	.30
Metabolism	62	24.5	55	23.0	.72	6	2.4	13	5.4	.08
Anorexia	42	16.6	41	17.2	.85	2	0.8	8	3.3	.04
Hyperglycemia	16	6.3	14	5.9	.84	0	0.0	3	1.3	.08
Musculoskeletal	3	1.2	3	1.3	.95	1	0.4	1	0.4	.98
Nervous system	19	7.5	37	15.5	.006	0	0.0	2	0.8	.15
Headache	9	3.6	12	5.0	.43	0	0.0	1	0.4	.32
Paresthesia	7	2.8	16	6.7	.04	0	0.0	1	0.4	.29
Psychiatric	1	0.4	1	0.4	.99	0	0.0	0	0.0	—
Renal	1	0.4	1	0.4	.99	1	0.4	0	0.0	.31
Respiratory	47	18.6	35	14.6	.25	8	3.2	12	5.0	.30
Cough	11	4.3	14	5.9	.41	0	0.0	1	0.4	.30
Dyspnea	32	12.6	20	8.4	.13	7	2.8	10	4.2	.40
Skin	13	5.1	13	5.4	.86	1	0.4	1	0.4	.98
Surgical	1	0.4	0	0.0	.31	1	0.4	0	0.0	.31
Vascular	19	7.5	19	7.9	.84	4	1.6	6	2.5	.47
Thromboembolism	8	3.2	9	3.8	.72	3	1.2	5	2.1	.44

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.
**P* value from stratified Mantel-Haenszel test.