Randomized Phase III Trial of Docetaxel Plus Carboplatin with or without Levofloxacin Prophylaxis in Elderly Patients with Advanced Non-small Cell Lung Cancer

The APRONTA Trial

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Purpose: To examine the effect of levofloxacin prophylaxis on infection rates during chemotherapy with docetaxel plus carboplatin in elderly patients with advanced non-small cell lung cancer.

Methods: In a randomized, double-blind, phase III study, patients (≥65 years) with untreated, histologically/cytologically proven stage IIIB/IV non-small cell lung cancer received docetaxel (75 mg/m^2) plus carboplatin (area under the curve 6) on day 1 every 3 weeks, plus once-daily levofloxacin (500 mg orally) or placebo on days 5 to 11. The primary end point was the rate of grade 3/4 infections or grade 1/2 infections treated with additional antibiotics. Secondary end points included overall infection rate, toxicity, overall survival, and progression-free survival.

Results: In total, 187 patients were randomized to levofloxacin (n = 95) or placebo (n = 92). The rate of grade 3/4 infections or grade 1/2 infections treated with additional antibiotics (intent-to-treat population) was 27.5% (95% confidence interval, 19.3–39.0%) for levofloxacin versus 36.7% (95% confidence interval, 27.1–48.0%) for placebo. Median time to first infection was 67 days for levofloxacin versus 46 days for placebo. Grade 3/4 infections occurred in 8.8% of patients in the levofloxacin group versus 26.7% for placebo. There was one grade 5 infection in each group. Grade ≥3 toxicities (levofloxacin versus placebo) included leukopenia (63.2 versus 52.2%), neutropenia (62.1 versus 51.1%), dyspnea (12.6 versus 8.7%), and pain (10.5 versus 9.8%). There was no significant difference in overall survival or progression-free survival between groups.

Conclusions: Levofloxacin prophylaxis reduces the rate of infection compared with placebo and is well tolerated in elderly patients receiving docetaxel plus carboplatin.

Key Words: Chemotherapy, Elderly, Levofloxacin, NSCLC, Prophylaxis.

(*J Thorac Oncol.* 2011;6: 2090–2096)

Lung cancer is the leading cause of cancer mortality in the United States.[1] The probability of developing invasive lung cancer rises from 0.03% in people aged ≤39 years to 6.74% in men and 4.61% in women aged ≥70 years.[1] Advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC) accounts for the majority of newly diagnosed cases.[2] Stage IV disease is associated with 5-year survival rates of <5%.[2]

Platinum-based combination chemotherapy regimens are currently used in the first-line setting for the treatment of advanced NSCLC,[3] but there are concerns about their tolerability in older patients.[4] In particular, there is increasing concern about hematologic toxicity in older patients treated with chemotherapy, because they are more likely than younger patients to experience febrile neutropenia and infection.[5]

In the phase III TAX 326 study of first-line chemotherapy in patients with stage IIIB/IV NSCLC, treatment with docetaxel in combination with carboplatin led to similar survival and response rates, but a more favorable safety profile and quality of life score compared with vinorelbine plus cisplatin.[6,7] Subgroup analysis of TAX 326 showed similar survival outcomes in elderly patients (aged ≥65 years) compared with younger patients.[8,9] Nevertheless, in this analysis, the rate of febrile neutropenia in patients aged ≥65 years who received docetaxel plus carboplatin was higher than in patients <65 years of age who received this regimen (7.0 versus 2.4%, respectively).[8] Elderly patients

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Disclosure: Katrin Roscher, MD, and Thorsten Salm, MD, are employed by Sanofi-Aventis Deutschland GmbH. Burkhard Deuss, MD, reports that ClinAssess GmbH, has served as CRO on this project.

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ISSN: 1556-0864/11/0612-2090

were also more likely to experience grade 3/4 infection during docetaxel plus carboplatin therapy.

One potential strategy to minimize the risk of infection during chemotherapy is the prophylactic use of an antibacterial agent. Levofloxacin is a once-daily, broad-spectrum oral fluoroquinolone antibiotic with proven clinical efficacy and acceptable tolerability in the treatment of bacteriologically documented infections of the respiratory and urinary tracts.[10] The prophylactic use of fluoroquinolone antibiotics in patients with cancer has been questioned because of the lack of supporting evidence from placebo-controlled trials and the potential for the development of bacterial resistance to fluoroquinolones.[11] However, previous phase III studies suggest that prophylaxis with levofloxacin is effective at reducing the incidence of bacterial infections in patients with cancer.[12,13]

Here, we report the results of the APRONTA trial, which examined the effect of levofloxacin prophylaxis on infection rates during chemotherapy with docetaxel plus carboplatin in older patients (≥65 years) with advanced NSCLC.

PATIENTS AND METHODS

This randomized, double-blind, placebo-controlled phase III trial compared the efficacy and tolerability of docetaxel plus carboplatin with versus without prophylactic levofloxacin in patients aged ≥65 years with previously untreated histologically or cytologically proven stage IIIB/IV NSCLC.

The primary end point was the rate of grade 3/4 infections or grade 1/2 infections treated with additional antibiotics in the intent-to-treat (ITT) population within the period from the first administration of antibiotic or placebo until the first follow-up visit 4 weeks after the final therapy cycle. Secondary end points included toxicity, response rate, 1-year survival, overall survival (OS), progression-free survival (PFS), and overall infection rate.

Patient Selection

Patients were required to meet the following inclusion criteria: age ≥65 years; inoperable histologically or cytologically proven stage IIIB/IV NSCLC; no prior chemotherapy for advanced disease; ≥1 lesion measurable by computed tomography or radiography; Eastern Cooperative Oncology Group performance status ≤2; life expectancy ≥12 weeks; and normal cardiac, renal, hepatic, and hematologic function (neutrophils $\geq 2 \times 10^9$/L; aspartate aminotransferase and alanine aminotransferase ≤1.5 × upper limit of normal [ULN]; alkaline phosphatase ≤2.5 × ULN; platelets $\geq 100 \times 10^9$/L; total bilirubin ≤ULN; creatinine ≤1.5 × ULN). All patients had to provide written informed consent before study entry.

Patients were excluded from the study if they had active infection or had received antibiotics within 72 hours before enrollment; a history of a second malignancy (except basal cell carcinoma of the skin or curatively treated carcinoma in situ of the cervix); maintenance treatment with corticosteroids or other immunosuppressive agents; concurrent radiation therapy or other tumor-specific therapy; preexisting neuropathy (sensory or motor) grade 2 according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0; central nervous system metastases; epilepsy; tendon disease; heart failure; or any other serious medical condition.

Treatment Plan

Patients were randomized 1:1 to receive docetaxel (75 mg/m^2 intravenously [IV], day 1) plus carboplatin (area under the curve 6, IV, day 1) every 3 weeks plus either placebo or levofloxacin (500 mg orally) once daily on days 5 to 11 of each 3-week cycle. Patients were to receive four to six cycles of treatment unless tumor progression or unacceptable toxicity occurred, or the patient withdrew their consent. Treatment could continue beyond six cycles at the physician's discretion without further administration of levofloxacin or placebo.

Toxicity was assessed during the treatment period according to NCT-CTC Version 3.0. Therapy could be delayed because of toxicity for a maximum of 3 weeks. If a delay of longer than 3 weeks was required, the patient was withdrawn from the study. The chemotherapy dose could also be reduced if considered necessary because of toxicity (docetaxel reduced to 60 mg/m^2 and carboplatin reduced to area under the curve 4.5 in one step). Reescalation to the original dose was at the physician's discretion. Patients were allowed one further dose reduction after reescalation; beyond that their participation in the study was discontinued. If a grade 3/4 infection, or a lower grade infection requiring systemic antibiotic therapy, was observed, chemotherapy was continued according to protocol but the antibiotic prophylaxis/placebo administration was stopped. Infections requiring systemic antibiotic therapy were treated at the discretion of the physician. Patients who developed grade 4 neutropenia that lasted for more than 7 days or that was accompanied by fever were treated with a nonfluoroquinolone antibiotic and received prophylactic granulocyte colony-stimulating factor during the subsequent treatment cycles. All patients received premedication with oral dexamethasone (8 mg twice daily), or an equivalent dose of corticosteroids, for 2.5 days starting 24 hours before docetaxel administration. An equivalent IV dose of dexamethasone was administered 30 minutes before docetaxel infusion. Antiemetics were given as necessary.

Baseline and Treatment Evaluations

Demographics, disease characteristics, laboratory tests, and image-guided procedures were recorded at baseline. Infections were classified based on NCI-CTC Version 3.0 and were defined as any occurrence with signs of localized infection, with or without fever (>38°C), and with or without microbiologic documentation, and septicemia verified by microbiologic testing (modified according to the criteria of the German Society of Hematology and Oncology).[14] The infection rate was assessed during the observation period between the first administration of antibiotic/placebo until the first follow-up visit 4 weeks after administration of the final treatment cycle.

Tumor evaluation was performed according to Response Evaluation Criteria in Solid Tumors[15] following every second cycle of chemotherapy. OS was defined as the time between randomization and death, and PFS was defined as

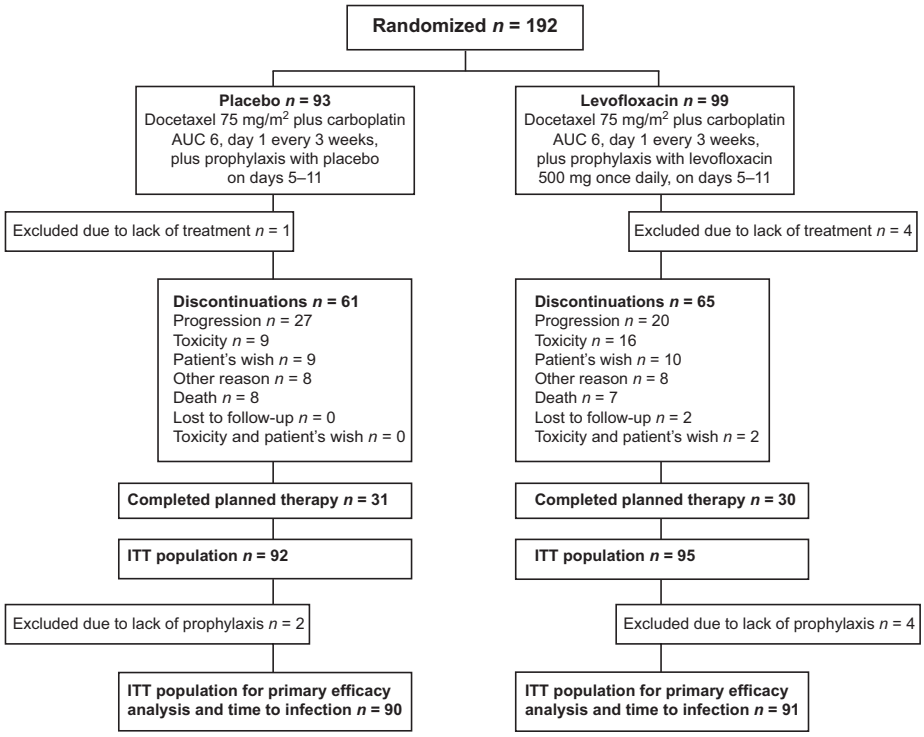

FIGURE 1. Patient flow. AUC, area under the curve; ITT, intent-to-treat.

the time between the first administration of study medication and the first evidence of progression or death.

Safety was evaluated by the number of adverse events (including outcome status) and the number of NCI-CTC toxicities after every chemotherapy cycle and every 3 months during follow-up. Serious adverse events were defined as those resulting in death, and those that were life threatening, required hospital treatment or prolonged hospitalization, resulted in disability, or were considered to be of medical significance. Laboratory parameters, including hematology, serum chemistry, and creatinine clearance, were assessed before each new treatment cycle, and blood counts were monitored weekly.

Statistical Methods

A sample size of 200 patients was considered to be sufficient based on estimated rates of infection of 20% in the placebo group and 5% in the levofloxacin group (two-sided test with $\alpha = 0.05$ and $\beta = 0.20$) and the expected follow-up loss of approximately 10%.

Descriptive statistical methods were used and included frequency counts and summary statistics with mean, SD, median, range, and first and third quartiles. Comparisons between the treatment groups were performed using Fisher exact test; 95% confidence intervals (CIs, exact method) were provided for the rates of infection. Kaplan–Meier survival analyses and log-rank tests were conducted for time-to-event variables.

The primary analysis population was the ITT population, which included all randomized patients who received at least one administration of prophylaxis with levofloxacin or placebo. Tumor response was evaluated in all patients who received at least one complete course of docetaxel. The safety population comprised all patients who received at least one cycle of docetaxel therapy. Additional analyses were conducted on November 28, 2008, for the ITT population and 11 subgroups. Results from the subgroup analysis according to age ($\leq$70 years or $>$70 years) are presented here.

RESULTS

Patients

Overall, 192 patients were enrolled at 26 centers in Germany between May 7, 2004, and February 18, 2008. Patients were randomized to docetaxel plus carboplatin and either levofloxacin ($n = 99$) or placebo ($n = 93$) (Figure 1); five patients received no treatment and were therefore excluded from the ITT population. Overall, 30 of 95 patients (32%) in the levofloxacin group and 31 of 92 patients (34%) in the placebo group completed the study. Disease progression was the most frequent cause of study discontinuation in both groups. The median number of treatment cycles was 4 in each treatment group.

Demographic and baseline disease characteristics were mostly well balanced between the two treatment groups (Table 1), with the exception of Eastern Cooperative Oncology Group performance status (slightly worse in the placebo group) and disease stage (a higher proportion of patients with stage IV disease in the placebo group). More than 40% of patients in each group had lymph node involvement and more than 10% had liver metastases.

TABLE 1. Baseline Characteristics (Intent-to-Treat Population)

Baseline Characteristic	Placebo ($n = 92$)	Levofloxacin ($n = 95$)
Mean age, yr (range)	70.7 (59–83)	70.8 (62–79)
Sex, *n* (%)		
Male	74 (80.4)	76 (80.0)
Female	18 (19.6)	19 (20.0)
ECOG performance status, *n* (%)		
0	28 (30.4)	40 (42.1)
1	56 (60.9)	47 (49.5)
2	8 (8.7)	8 (8.4)
Diagnosis, *n* (%)		
Adenocarcinoma	45 (48.9)	50 (52.6)
Squamous cell carcinoma	36 (39.1)	28 (29.5)
Other NSCLC	8 (8.7)	10 (10.5)
Large cell carcinoma	3 (3.3)	7 (7.4)
Disease stage, *n* (%)		
IIIB	16 (17.4)	31 (32.6)
IV	76 (82.6)	63 (66.3)
Unknown	0	1 (1.1)
Prior therapy, *n* (%)		
None	76 (82.6)	77 (81.1)
Surgery	10 (10.9)	9 (9.5)
Radiotherapy	3 (3.3)	6 (6.3)
Radiotherapy for metastases	3 (3.3)	5 (5.3)
Laser therapy	1 (1.1)	2 (2.1)

ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

Infection

For the primary efficacy end point, six patients without prophylaxis with placebo/levofloxacin were excluded from the ITT population. The rate of grade 3/4 infections or grade 1/2 infections treated with additional antibiotics (the primary end point) was 27.5% (95% CI, 19.3–39.0%) for levofloxacin and 36.7% (95% CI, 27.1–48.0%) for placebo (Table 2).

The infection rate was higher in the placebo group compared with the levofloxacin group, but this difference did not reach statistical significance (Fisher exact test, $p = 0.263$; Table 3). The median (range) time to first infection was 46 (2–411) days for placebo and 67 (0–279) days for levofloxacin. A time to first infection of 0 days indicates an infection with onset on the first day of antibiotic prophylaxis.

Additional analysis revealed that the greatest between-group difference in median time to first infection was in the subgroup of patients aged >70 years (69 and 27 days for levofloxacin and placebo, respectively; Table 3).

A larger proportion of patients in the placebo group experienced grade 3/4 infections than in the levofloxacin group (26.7 versus 8.8%, respectively; Table 2). There was one case of grade 5 infection in each group. One patient in the placebo group experienced fever, grade 3/4 neutropenia, and grade 5 sepsis, and one patient in the levofloxacin group presented with fever, grade 3/4 urinary tract infection, grade 4 candidiasis, and grade 5 urosepsis. The most common infection was pneumonia (21.7 and 11.6% in the placebo and levofloxacin groups, respectively) (Table 4).

Fever was experienced by 23.9% of patients in the placebo group and 16.8% of those in the levofloxacin group. Grade 3/4 neutropenia was reported as a symptom in 18.5% of patients in the placebo group versus 16.8% in those treated with levofloxacin.

Efficacy

The median follow-up was 8 months for both treatment groups combined. Overall tumor response rates (complete or partial response) were 30.4 and 29.5% in the placebo and levofloxacin groups, respectively ($p = 1.0$ based on Fisher exact test).

At the data cut-off for the final analysis (November 28, 2008), there had been 64 deaths in the placebo group and 64 in the levofloxacin group. No significant improvements in OS were observed with levofloxacin prophylaxis compared with placebo. The median OS was 314 days in the placebo group and 307 days in the levofloxacin group and hence was

TABLE 2. Rates of Infection (Intent-to-Treat Population)

	No. of Patients With Infection (%)	
Grade of Infection	Placebo ($n = 90$)[a]	Levofloxacin ($n = 91$)[a]
1 + additional antibiotic therapy	0 (0)	5 (5.5)
2 + additional antibiotic therapy	8 (8.9)	11 (12.1)
3	19 (21.1)	7 (7.7)
4	5 (5.6)	1 (1.1)
5[b]	1 (1.1)	1 (1.1)
All	33 (36.7)	25 (27.5)
95% CI	27.1–48.0	19.3–39.0

[a] Six patients (two placebo, four levofloxacin) were not included in the analysis because they did not receive prophylaxis with placebo/antibiotic.
[b] Only the highest grade was documented for each event.
CI, confidence interval.

TABLE 3. Infection Rates and Time to First Infection (Intent-to-Treat Population)

Treatment Group	Patients With Infection, % (95% CI)	Median (Range) Time to First Infection,[a] d
ITT analysis[b]		
Placebo ($n = 90$)	36.7 (27.1–48.0)	46 (2–411)
Levofloxacin ($n = 91$)	27.5 (19.3–39.0)	67 (0–279)
Additional analysis		
Placebo ($n = 90$)[b]		
≤70 yr ($n = 49$)	36.7 (24.0–52.7)	69 (2–125)
>70 yr ($n = 41$)	36.6 (22.1–53.1)	27 (2–411)
Levofloxacin ($n = 91$)[b]		
≤70 yr ($n = 44$)	29.6 (17.2–46.1)	65 (0–279)
>70 yr ($n = 47$)	25.5 (14.6–41.9)	69 (1–154)

[a] Time between first prophylactic treatment with antibiotics/placebo and the start of infection.
[b] Six patients (two placebo, four levofloxacin) were not included in the analysis because they did not receive prophylaxis with placebo/antibiotic.
CI, confidence interval.

TABLE 4. Infection Events (Intent-to-Treat Population)[a]

	No. of Patients With Infection, *n* (%)			
	Placebo (*n* = 92)		Levofloxacin (*n* = 95)	
Grade of Infection	All Grades	Grade ≥3	All Grades	Grade ≥3
Pneumonia	20 (21.7)	12 (13.0)	11 (11.6)	6 (6.3)
Sepsis	4 (4.3)	4 (4.3)	1 (1.1)	1 (1.1)
Febrile neutropenia	3 (3.3)	3 (3.3)	4 (4.2)	4 (4.2)
Urinary tract infection	2 (2.2)	0	3 (3.2)	1 (1.1)
Acute exacerbation of chronic bronchitis	1 (1.1)	0	1 (1.1)	0
Other	15 (16.3)	4 (4.3)	22 (23.2)	5 (5.3)
Unknown	2 (2.2)	—[a]	1 (1.1)	—[b]

[a] Includes six patients (two placebo, four levofloxacin) who did not receive prophylaxis.
[b] No. of patients unknown because the grade of infection was not documented.

comparable for both treatment groups (hazard ratio, 0.83; 95% CI, 0.58–1.17; $p = 0.28$; Figure 2).

PFS results for the two groups were similar (84.8% for placebo versus 83.2% for levofloxacin). Median PFS was greater in the levofloxacin group (121 days for placebo versus 165 days for levofloxacin), but this difference did not reach statistical significance (hazard ratio, 0.82; 95% CI, 0.60–1.13; $p = 0.22$; Figure 3). If deaths occurring later than 1 year after randomization are censored, the 1-year OS rate was 33.7% in the placebo group and 36.8% in the levofloxacin group.

Toxicity

Grade ≥3 toxicities included leukopenia (52.2 placebo versus 63.2% levofloxacin), neutropenia (51.1 versus 62.1%), dyspnea (8.7 versus 12.6%), thrombocytopenia (12.0 versus 7.4%), diarrhea (10.9 versus 3.2%), pain (9.8 versus 10.5%), anemia (7.6 versus 2.1%), mucositis (0 versus 5.3%), asthenia (4.3 versus 1.0%), febrile neutropenia (3.3 versus 4.2%),

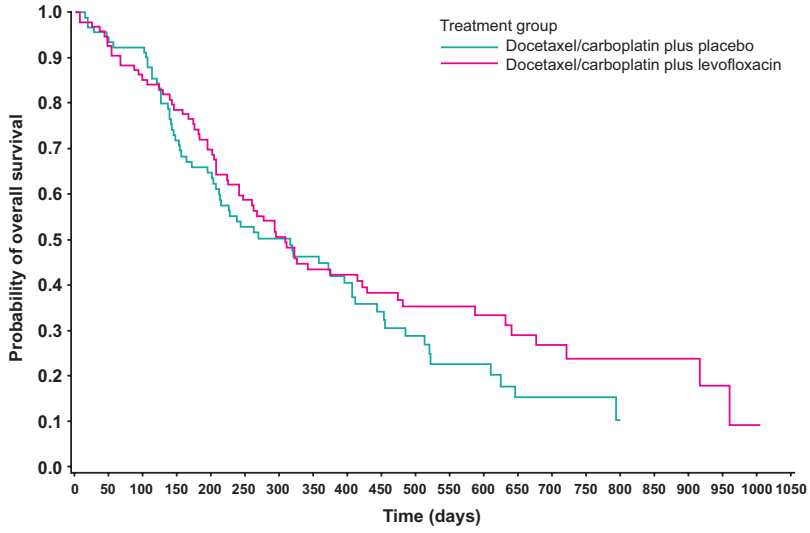

FIGURE 2. Kaplan-Meier analysis of overall survival (intent-to-treat population). Median overall survival: placebo, 314 days; levofloxacin, 307 days; hazard ratio, 0.83 (95% confidence interval, 0.58–1.17); log rank, $p = 0.28$.

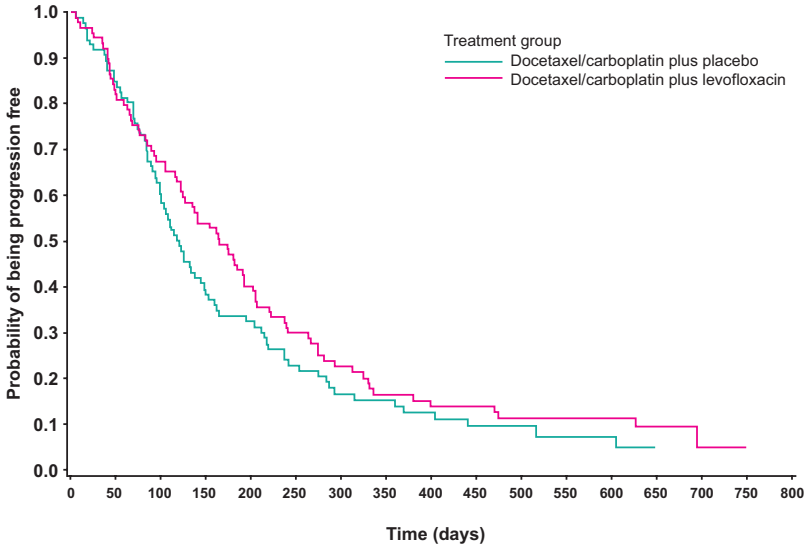

FIGURE 3. Kaplan-Meier analysis of progression-free survival (intent-to-treat population). Median progression-free survival: placebo, 121 days; levofloxacin, 165 days; hazard ratio, 0.82 (95% confidence interval, 0.60–1.13); log rank, $p = 0.22$.

nausea (1.1 versus 3.2%), vomiting (0 versus 3.2%), and candidiasis (0 versus 1.1%). In the subgroup of patients aged ≥70 years, the most common grade ≥3 toxicities were neutropenia (70% placebo versus 59.6% levofloxacin), leukopenia (56.1 versus 59.6%), diarrhea (19.5 versus 2.1%), dyspnea (7.3 versus 17%), and pain (14.6 versus 8.5%).

DISCUSSION

Infections as sequelae of hematologic toxicity remain a leading cause of death in patients receiving chemotherapy for advanced NSCLC, despite improvements in survival rates through the use of platinum-based combination regimens.[16] This phase III randomized placebo-controlled trial demonstrated that the prophylactic use of levofloxacin with first-line docetaxel/carboplatin chemotherapy is well tolerated and is associated with a reduction in the rate of infection compared with placebo prophylaxis in elderly patients with advanced NSCLC. Furthermore, the median time to first infection was prolonged in the levofloxacin group (67 versus 46 days for levofloxacin versus placebo). No survival advantage was demonstrated in patients who received levofloxacin prophylaxis, but median OS was comparable with that reported in other studies of docetaxel/carboplatin chemotherapy in elderly patients with advanced NSCLC.[8,9]

Fluoroquinolones are widely used for prophylaxis during chemotherapy.[17] However, this practice is not recommended in the most recent guidelines published by the Infectious Diseases Society of America.[11] This is largely because of the lack of data from randomized trials and the failure to demonstrate a survival advantage with this approach. Several phase III studies have now shown that prophylaxis with levofloxacin is effective at reducing the incidence of bacterial infections and febrile neutropenia in patients with solid tumors or lymphoma.[12,13] In addition, a meta-analysis of patients with neutropenia found that fluoroquinolone prophylaxis was associated with a significant reduction in the incidence of febrile episodes and a trend toward decreased mortality compared with patients who received no prophylaxis.[18] Other concerns that remain to be addressed include the potential for the development of bacterial resistance,[19] the opportunity for fungal infections, and the issue of whether prophylactic use of fluoroquinolones will later impact on the choice of empiric therapy for infections. Defining the population of patients most likely to benefit from prophylaxis would be valuable to ensure appropriate use of antibiotics and to preserve their utility for empiric therapy.

Older patients with advanced NSCLC are particularly vulnerable to the effects of chemotherapy, which include hematologic toxicity and associated infections. The subgroup of patients aged >70 years in this study demonstrated a median time to infection of 69 days with levofloxacin versus 27 days with placebo. In patients ≤70 years, the corresponding values were 65 days for levofloxacin versus 69 days for placebo. No clinically noteworthy differences in toxicity were observed in the subgroup of patients >70 years of age who received prophylaxis compared with the overall population. Further studies of subgroups of patients with different risk factors for infection will be useful to define the patient populations that will benefit most from levofloxacin prophylaxis.

The rates of febrile neutropenia reported in this study are comparable to rates reported in other studies of docetaxel/carboplatin in older patients with advanced NSCLC.[8] Rates of infection for patients who received levofloxacin were lower than those reported in the TAX 326 subgroup analysis.[8] Grade 3/4 infections were reported in our study by 26.1% of the placebo group versus 8.4% of the levofloxacin group. For comparison, in the subgroup analysis of elderly patients (≥65 years) in the TAX 326 study who received docetaxel/carboplatin, the rate of grade 3/4 infections was 15.4%.[8] There was one death as a result of infection (grade 5) in each treatment group in this study.

The emergence of resistance to levofloxacin was not monitored in this study. However, the development of bacterial resistance was not expected to be an issue because levofloxacin was only administered for 7 days. This may be worth assessing in future studies to guide appropriate use of fluoroquinolones for antibacterial prophylaxis in patients with cancer.

In clinical practice, older patients with advanced NSCLC are less likely to receive chemotherapy and are often undertreated. This may contribute to the lower survival rates reported in this group of patients.[20] Treatment strategies are needed to minimize the adverse effects of chemotherapy in these patients. Larger studies of the use of prophylactic antibiotics are warranted and may show a survival benefit because of reduction in infection-related mortality, which this study was not designed to demonstrate.

In conclusion, this study has demonstrated that docetaxel/carboplatin chemotherapy with levofloxacin prophylaxis is well tolerated in elderly patients with advanced NSCLC and is associated with a lower rate of infection compared with the chemotherapy regimen given without levofloxacin prophylaxis. Nevertheless, additional prophylactic use of granulocyte macrophage colony-stimulating factor should be considered in some patients to avoid dose reductions of chemotherapy and cases of febrile neutropenia, especially in those with comorbidities and limited organ function.

ACKNOWLEDGMENTS

Supported by Sanofi-aventis.

The authors thank Neil Anderson, PhD, of Adelphi Communications Ltd, for providing editorial assistance.

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