Safety and efficacy of weekly nab®-paclitaxel in combination with carboplatin as first-line therapy in elderly patients with advanced non-small-cell lung cancer


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Received 11 May 2012; revised 24 July 2012; accepted 25 July 2012

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Background: This analysis evaluates safety and efficacy in elderly (≥70 years old) versus younger patients enrolled in a phase III advanced non-small-cell lung cancer (NSCLC) trial.

Patients and Methods: Untreated stage IIIb/IV patients with PS 0/1 were randomly assigned (1:1) to carboplatin AUC6, day 1 every 3 weeks, and either nab-paclitaxel (Abraxane) 100 mg/m² weekly (nab-P/C) or solvent-based paclitaxel (Taxol) 200 mg/m² day 1 every 3 weeks (sb-P/C). The primary end-point was overall response rate (ORR).

Results: Fifteen percent of 1052 enrolled patients were elderly: nab-P/C, n = 74; sb-P/C, n = 82. In both age cohorts, the ORR was higher with nab-P/C versus sb-P/C (age ≥70: 34% versus 24%, P = 0.196; age <70: 32% versus 25%, P = 0.013). In elderly patients, progression-free survival (PFS) trended in favor of nab-P/C (median 8.0 versus 6.8 months, hazard ratio (HR) 0.687, P = 0.134), and overall survival (OS) was significantly improved (median 19.9 versus 10.4 months, HR 0.583, P = 0.009). In younger patients, PFS (median 6.0 versus 5.8 months, HR 0.903, P = 0.256) and OS (median 11.4 versus 11.3 months, HR 0.999, P = 0.988) were similar in both arms. Adverse events were similar in both age groups, with less neutropenia (P = 0.015), neuropathy (P = 0.001), and arthralgia (P = 0.029), and increased anemia (P = 0.007) with nab-P/C versus sb-P/C.

Conclusions: In elderly NSCLC patients, nab-P/C as first-line therapy was well tolerated and improved the ORR and PFS, with substantially longer OS versus sb-PC.

Key words: advanced NSCLC, elderly, first-line therapy, nab-paclitaxel

introduction

Elderly patients with advanced non-small-cell lung cancer (NSCLC) are typically undertreated. Recent reports suggest that only a minority receive therapy [1–3]. Platinum-based doublets, i.e. carboplatin or cisplatin with a third-generation agent, including taxanes, gemcitabine, vinorelbine, and pemetrexed, are the standard of care for advanced NSCLC. Older patients often present with poor performance status and/or comorbidities; consequently, many receive only best supportive care. Because of anticipated toxic effects, elderly patients are often under-represented in clinical trials, and new therapeutic options for them are limited. The median age in large clinical trials is 59–63 years [4], whereas the median age for all patients diagnosed with NSCLC is 71 years [5]. As most patients with NSCLC are ≥70 years old, more effective and better-tolerated therapeutic options for the elderly are needed.

Albumin-bound paclitaxel [nab-paclitaxel (Abraxane)] Celgene, Summit, NJ, USA), with a mean particle size of 130 nm, was developed to improve the therapeutic index of paclitaxel. nab-Paclitaxel is approved for the treatment of metastatic breast cancer and has been evaluated in phase I/II studies in NSCLC both as a single agent [6] and in combination with carboplatin [7, 8], exhibiting promising efficacy and tolerability. In a recently completed phase III study, weekly nab-paclitaxel plus every-3-week carboplatin (nab-P/C) was compared with standard, every-3-week regimen of solvent-based (sb) paclitaxel (Taxol, Bristol-Myers Squibb, New York, NY, USA) plus carboplatin (sb-P/C) as first-line treatment in patients with advanced NSCLC. Compared with sb-P/C, nab-P/C produced significantly higher overall response rates (ORR, 33% versus 25%, P = 0.005) and a nonsignificant 1-month improvement in median overall survival (OS, 12.1 versus 11.2 months, P = 0.271) [8]. This exploratory analysis investigates the safety and efficacy in the elderly subgroup from the phase III study [8].

materials and methods

This international, multicenter, randomized, phase III study in patients with advanced NSCLC compared the efficacy and safety of nab-paclitaxel, administered as a 30-minute infusion at a dose of 100 mg/m² on days 1, 8, and 15 followed by carboplatin at an AUC of 6 mg/min/ml (per Calvert formula) [9] given on day 1 every 21 days with the efficacy of sb-paclitaxel 200 mg/m², infused over 3 hours, plus carboplatin AUC 6, both given on day 1 every 21 days. Patients were randomly assigned (1:1) to nab-P/C or sb-P/C and stratified by age (<70 versus ≥70 years), stage disease (IIIB versus IV), gender (male versus female), histology (squamous versus adenocarcinoma versus others), and geographic region (Canada/USA versus Russia/Ukraine versus Japan versus Australia). Six cycles of therapy were encouraged; treatment beyond 6 cycles was permissible at the investigators’ discretion in the absence of progressive disease or unacceptable toxicity.

Eligible adults had histologically or cytologically confirmed stage IIIB (with or without pleural effusion) or IV NSCLC [10], measurable by Response Evaluation Criteria In Solid Tumors (RECIST) 1.0 [11], an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, and a life expectancy of >12 weeks. Patients were previously untreated for metastatic disease and received no radiotherapy within 4 weeks of enrollment. Prior adjuvant chemotherapy was permitted if completed ≥12 months before study enrollment. Patients were excluded from the study if they had untreated or symptomatic brain metastases.

This study was approved by the independent ethics committees of the participating medical institutions and was conducted in compliance with the World Medical Association Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization [12]. A written informed consent was obtained from all patients before study initiation.

assessment of elderly subset

The objectives of this analysis were to investigate the efficacy and safety of nab-P/C and sb-P/C in elderly patients (≥70 years old) enrolled in the phase III study and to compare the results with younger patients.

The primary end-point of the phase III study was ORR (rate of confirmed complete or partial responses), determined by centralized, independent radiologic review according to RECIST. Tumors were assessed by spiral computed tomography scans every 6 weeks during therapy. For patients whose disease had not progressed by the end of treatment, repeat imaging continued every 6 weeks until tumor progression. Secondary efficacy analyses included progression-free survival (PFS) and OS. Safety and tolerability were monitored through reporting of adverse events (AEs),
laboratory abnormalities, and incidence of dose modifications, dose interruptions, and/or premature discontinuations of study drug. Neuropathy, pain in hands/feet, hearing loss and edema were also reported by patients at baseline, day 1 of each cycle, and after completion of therapy using the Functional Assessment of Cancer Therapy (FACT)-taxane v4.0 scale.

statistical methods
As age was a stratification factor specified in the protocol, the analysis of the effect of age on the outcome in the context of the phase III randomized trial was planned. All randomized patients were evaluated for efficacy [intent-to-treat (ITT) population]. The percentage of patients with objective ORR [95% confidence interval (CI)] was summarized for patients <70 and ≥70 years old. PFS and OS were analyzed using Kaplan–Meier methods. Regression analysis was conducted based on the Cox proportional hazards models to adjust for the effects of baseline characteristics. Treatment interaction was assessed using a logistic regression model that estimated the effects of the treatment regimen, age, and treatment regimen by age interaction on efficacy parameters.

All patients who received ≥1 dose of study drug (treated population) were evaluated for safety. The Fisher exact test and the Cochran–Mantel–Haenszel test were used to evaluate treatment-related AEs (graded using National Cancer Institute Common Terminology Criteria for Adverse Events v3.0) for differences between the treatment arms and between patients <70 and ≥70 years old. The FACT-taxane scale was analyzed by descriptive statistics, including mean change from baseline at each cycle.

results
patients
Fifteen percent (156/1052) of all randomized ITT patients enrolled between December 2007 and July 2009 in the phase III study were elderly: nab-P/C, n = 74 and sb-P/C, n = 82. Seventy-three and eighty-one elderly patients were treated in the nab-P/C and sb-P/C arms, respectively. Baseline characteristics were generally well balanced between the treatment arms; however, the nab-P/C arm had more patients with squamous histology and more previous smokers (Table 1). Similar to the entire study population, the majority of elderly patients was male (72%) and Caucasian (71%) with baseline ECOG performance status of 1 (73%) and stage IV disease (83%). Twenty-eight percent of elderly patients were from the United States, 27% from Russia, and 20% from Japan. The most common histologies in the elderly patients were adenocarcinoma (49%), followed by squamous cell carcinoma (42%). Patients with large-cell carcinoma and other undifferentiated histologies constituted the other 10%. The median smoking history was 50 pack-years (range 9–70) and was balanced between both treatment arms. Only 5% of elderly patients received chemotherapy before randomization, consistent with the eligibility criteria.

At the time of the database lock, 105 of the 156 elderly patients (67%) had died, 44 (59%) in the nab-P/C arm and 61 (74%) in the sb-P/C arm. The median follow-up of all patients was 21 months (nab-P/C, 22 months; sb-P/C 21 months).

efficacy results of patients <70 and ≥70 years of age
overall response rate
In the elderly population, independent radiologic assessment revealed a higher ORR in the nab-P/C versus sb-P/C arms (34% versus 24%, P = 0.196, response rate ratio = 1.385; Table 2). In patients <70 years old, a significant improvement in ORR was observed (32% versus 25%, respectively, P = 0.013). No interaction between the treatment effect on ORR and age was observed (P = 0.814).

progression-free survival
In the elderly population, a nonsignificant trend toward improved PFS in the nab-P/C versus sb-P/C arms was observed. The median PFS was 8.0 months (95% CI 6.0–11.0 months) with nab-P/C versus 6.8 months (95% CI 4.3–9.5 months) with sb-P/C, P = 0.134, HR 0.687 (Table 2, Figure 1). However, there was no difference in PFS in patients <70 years old: median 6.0 months (95% CI 5.5–6.9) with nab-P/C versus 5.8 months (95% CI 5.6–6.7) with sb-P/C, P = 0.256, HR 0.903 (Table 2). No interaction was observed for age and the treatment effect on PFS (P = 0.727).

overall survival
In the elderly population, the median OS almost doubled: 19.9 months (95% CI 12.7–22.3 months) with nab-P/C versus 10.4 months (95% CI 8.6–13.6) with sb-P/C, P = 0.009, HR 0.583 (Table 2, Figure 1). No differences in median OS were observed in patients <70 years old: 11.4 months (95% CI 10.3–12.6) with nab-P/C versus 11.3 months (95% CI 10.3–12.9) with sb-P/C, P = 0.988, HR 0.999 (Table 2). A significant interaction between age and the treatment effect on OS was observed (P = 0.018).

treatment exposure in patients ≥70 years of age
All elderly patients except 1 in the nab-P/C arm had discontinued therapy at the time of the data cut-off for the final analyses. The common reasons for discontinuation in the nab-P/C and sb-P/C arms were progressive disease (43% versus 38%, respectively), patient discretion (22% versus 15%, respectively), unacceptable toxicity without progressive disease (17% in both arms), and investigator’s discretion (11% versus 22%, respectively).

The median number of cycles administered was 5.0 with nab-P/C versus 6.0 with sb-P/C. Twenty-two percent of patients in both arms received more than 6 cycles of treatment. The median cumulative taxane dose administered was 1150 and 1000 mg/m² in the nab-P/C and sb-P/C arms, respectively. The planned and delivered weekly dose intensities were 100 and 73.4 mg/m²/week in the nab-P/C arm and 67 and 63.2 mg/m²/week in the sb-P/C arm. The median cumulative carboplatin dose administered was 2428 and 2664 mg in the nab-P/C and sb-P/C arms, respectively; and the median dose intensities were 127.7 and 170.5 mg/week, respectively. Fifty-five percent and 37% of patients in the nab-P/C versus sb-P/C arms, respectively, had a taxane dose reduction, primarily due to neutropenia (34% versus 20%, respectively), thrombocytopenia (27% versus 5%, respectively), anemia (7% versus 0%, respectively), and sensory neuropathy.
Eighty-four percent and 56% of patients in the nab-P/C versus sb-P/C arms, respectively, had a taxane dose delayed, mainly due to AEs (62%), including neutropenia (58% versus 20%, respectively), thrombocytopenia (38% versus 15%, respectively), anemia (15% versus 1%, respectively), leukopenia (14% versus 1%, respectively), and sensory neuropathy (7% versus 14%, respectively). The number of carboplatin dose reductions, dose interruptions, and dose delays were similar to the number of taxane modifications in both arms.

Approximately 10% more elderly patients in the nab-P/C (61%) versus sb-P/C (50%) arms received second-line therapy; a similar percentage of patients <70 years old in each arm received second-line therapy (52% versus 55%, respectively). In the elderly population, the most commonly used second-line treatments were single agents; docetaxel (nab-P/C: 14%; sb-P/C: 7%), erlotinib (nab-P/C: 8%; sb-P/C: 4%).
null
neuropathy in patients ≥70 years of age

Neuropathy was measured by physician assessment and the patient-reported FACT-taxane questionnaire, both of which demonstrated consistently less cumulative neurotoxicity in favor of the nab-P/C arm. By physician assessment, the overall rate of neuropathy was significantly less with nab-P/C (53%) versus sb-P/C (67%; P = 0.001). Almost half of the elderly patients (47%) did not develop sensory neuropathy of any grade with nab-P/C versus 33% of patients with sb-P/C (P = 0.001). A significantly lower rate of grade ≥3 neuropathy was observed with nab-P/C versus sb-P/C (P = 0.007). Neuropathy occurred later during treatment in the nab-P/C versus sb-P/C arms; median time to onset of 48.0 versus 24.5 days (P = 0.002).

patient-reported FACT-taxane subscale results in patients ≥70 years of age

Most elderly patients completed FACT-taxane questionnaire at baseline (99%) and provided follow-up assessments (90%). Significant treatment effects favoring nab-P/C were noted for patient-reported neuropathy (4.99 versus 1.86, P < 0.001), pain in hands and feet (2.19 versus 0.7, P < 0.001), hearing loss (0.41 versus −0.13, P = 0.022), and edema subscales (1.16 versus 0.27, P = 0.004) (Figure 2).

discussion

In elderly patients with advanced NSCLC of all histologies, first-line nab-P/C therapy yielded a trend toward increased ORR and PFS and significantly improved OS compared with sb-P/C, with an improved tolerability profile. This outcome is particularly intriguing because this population, especially those with squamous histology, has limited therapeutic options. Even though the ORR was improved in patients <70 years of age, no survival differences between nab-P/C and sb-P/C were observed in patients <70 years of age.

It is unclear whether the apparent survival benefit in elderly patients was due to the intrinsic superiority of nab-paclitaxel.
versus standard paclitaxel, its reduced toxicity and heightened tolerability, or more frequent exposure to taxanes afforded by the weekly therapy. It is conceivable that the improvement in toxicity with nab-P/C, specifically in neuropathy and neutropenia, allowed for higher dose delivery and intensity and may have contributed to the apparent survival advantage. Alternatively, there may be an intrinsic benefit to weekly, metronomic taxane exposure versus more conventional, episodic (every-3-week) exposure. It has been speculated that weekly taxanes may have a cytotoxic as well as anti-angiogenic effect and that solvents may dampen the anti-angiogenic effects of taxanes [13]. However, in a phase III trial in metastatic breast cancer, comparing of nab-paclitaxel with sb-paclitaxel using the same schedule (every 3 weeks) in both arms, nab-paclitaxel produced superior efficacy, with significantly improved ORR and time-to-progression in all treated patients and OS in ≥second-line patients [14]. Furthermore, this hypothesis should have led to improved OS in all age groups, which was not observed. These results suggest that independent of schedule, other advantages of nab-paclitaxel may account for the improved efficacy observed in this trial in patients with advanced NSCLC. Importantly, elderly patients on the nab-P/C arm received more second-line treatment, possibly because they may have been in better shape due to a better tolerated first-line regimen with nab-P/C or perhaps due to better disease and symptom control as demonstrated by the improvement in ORR. Second line-therapy with docetaxel and erlotinib has been shown in phase III trials to improve survival results over best supportive care or placebo [15, 16]. The Kaplan–Meier survival curves continued to diverge late in the course of the study, suggesting that the higher percentages of second-line therapy in the nab-P/C arm of the elderly cohort may have played a role in the improved survival outcome (Figure 1). The lack of survival benefit in the <70 years old cohort may be explained in part by the similar percentages of second-line therapy in both treatment arms (52% and 55%). It is also notable that the sample size for patients ≥70 years old was smaller, ~1/5th of those <70 years old, which may have contributed to the differences in findings between the two age cohorts.

Finally, the AE profile in elderly patients mirrors that described for the ITT population [8] and in patients <70 years old. Significantly less grade ≥2 sensory neuropathy, arthralgia, and neutropenia were observed with nab-P/C versus sb-P/C; however, rates of anemia were significantly higher in the nab-P/C arm. Additionally, FACT-taxane scores showed a significantly better profile with respect to patient-reported neuropathy, pain, hearing, and edema subscales in patients receiving nab-P/C versus sb-P/C, indicating that the nab-P/C regimen was better tolerated by elderly patients. This is particularly promising in the older patient population because neuropathy has been dose limiting in taxane-based regimens [17]. This improvement is likely attributable, in part, to the weekly schedule of paclitaxel, which proved more tolerable in the elderly compared with paclitaxel given every 3 weeks. It is also possible that the lack of cremophor in nab-paclitaxel may have helped mitigate neuropathy since cremophor alone has also been demonstrated to cause neuropathy [18].

The improved survival and tolerability seen in the nab-P/C arm versus the sb-P/C arm may also be attributed to the unique activity of the albumin-bound paclitaxel particles. Albumin, a natural carrier of fatty acids, accumulates in tumors [19], and paclitaxel binds to albumin with high affinity [20], allowing paclitaxel to reach tumor cells efficiently and producing a linear pharmacokinetic profile [21]. The cremophor excipient in sb-paclitaxel traps paclitaxel in micelles, thereby reducing immediate bioavailability that could compromise efficacy and contribute to the nonlinear pharmacokinetics profile of sb-paclitaxel [21].

Although the sample size of the elderly population in this study is relatively small, it still included over 150 patients, roughly equivalent to the number of enrollees on the Elderly Lung Cancer Vinorelbine Italian Study trial, which first demonstrated a survival benefit for vinorelbine versus best supportive care [22]. In this regard, given the historical context of NSCLC trials focused on the elderly, the combination of nab-P/C looks particularly promising. Taxanes, either alone or in combination with platinum, have previously shown superiority to single agents, such as vinorelbine [23–26]. For instance, the West Japan Thoracic Oncology Group Trial randomized 182 patients 70 years of age and older to vinorelbine or docetaxel. Although there was no significant difference in median OS (14.3 versus 9.9 months, HR 0.78, 95% CI 0.56–1.09), docetaxel yielded an improved PFS (5.5 months versus 3.1 months; P < 0.001) and improved quality of life, with an improvement in overall disease-related symptom scores [23].

The use of platinum-doublet therapy remains controversial in elderly patients. Recently, Quoix et al. compared weekly sb-paclitaxel plus monthly carboplatin versus either single-agent vinorelbine or gemcitabine in patients 70 to 90 years old with performance status of 0–2 [27]. The ORR and median PFS and OS were significantly longer with doublet chemotherapy; median OS was 10.3 versus 6.2 months (HR 0.64, 95% CI 0.52–0.78; P < 0.0001). Survival at 1 year in the combination arm was 45% versus 25% in the monotherapy arm. However,
toxicity was greater in the combination arm, including more treatment-related deaths, 10 (4.4%) versus 3 (1.3%) in the monotherapy arm [27]. Survival results observed with weekly sb-P/C in the trial by Quoix et al. were very similar to those observed with sb-P/C in this trial, in which sb-paclitaxel was administered every 3 weeks. The promising results demonstrating a survival advantage for nab-P/C versus sb-P/C need to be substantiated by further phase III testing.

In summary, in elderly patients with advanced NSCLC, nab-P/C led to improved ORR and PFS, with significantly longer OS versus sb-P/C. Although this is a subset analysis, the nab-P/C combination should be considered among first-line treatment options for the elderly; further study of this regimen in this population is planned.

acknowledgements

The authors thank all participating sites and investigators for their support with the clinical study and Paul Bhar, Celgene, for biostatistical analyses. Medical writing assistance was provided by Anita N. Schmid, PhD, Celgene. The authors are fully responsible for content and editorial decisions for this manuscript.

data

This work was supported by Celgene Corporation, Summit, NJ, USA.

disclosures

MAS received grant for research, honorarium/consulting fee, and served as an adviser for Celgene. CJL received honorarium/consulting fee and has served as an adviser for Celgene. MFR is an employee and stockholder of Celgene. HZ is an employee of Celgene. All remaining authors have declared no conflicts of interest.

references


