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Exploring Therapeutic Decisions in Elderly Patients with Non-Small Cell Lung Cancer: Results and Conclusions from North Central Cancer Treatment Group Study N0222

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Abstract

How do oncologists choose therapy for the elderly? Oncologists assigned patients aged 65 years or older with incurable non-small cell lung cancer to: (a) carboplatin (AUC = 2) + paclitaxel 50 mg/m² days 1, 8, 15 (28-day cycle × 4) followed by gefitinib; or (b) gefitinib 250 mg/day. With (a), 12 of 34 were progression-free at 6 months; median time to cancer progression was 3.9 months. With (b), the same occurred in 11 of 28 patients with the latter being 4.9 months. The most common reason for conventional chemotherapy was oncologists' opinion that the cancer was aggressive, and for gefitinib alone, patients' reluctance to receive chemotherapy. Interestingly, age had no influence.

Keywords

Elderly cancer patients; Non-small cell lung cancer; Carboplatin; Gefitinib

DECLARATION OF INTEREST

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INTRODUCTION

Over half of patients diagnosed with lung cancer are 65 years of age or older (1). The challenges of providing conventional chemotherapy to such elderly patients are well recognized and include the management of adverse events, such as higher rates of more severe myelosuppression (2). Yet, despite such challenges, previous studies show that elderly patients can gain clinical benefits from either conventional systemic chemotherapy or from more targeted therapies, such as epidermal growth factor receptor inhibitors (3, 4).

The number of therapeutic options for non-small cell lung cancer patients has increased steadily over the years, but oncologists still struggle to decide how best to treat older patients with this malignancy. How and why do oncologists choose conventional chemotherapy versus other more targeted agents? What clinical factors weigh into this decision-making?

The current study attempted to explore the two questions posed above. This report describes clinical outcomes from two parallel, non-randomized phase II trials, both of which were included in the same study protocol, one of which examined conventional chemotherapy upfront followed by an epidermal growth factor receptor inhibitor, and the other of which tested only an epidermal growth factor receptor inhibitor. In the context of these two parallel trials, this report provides descriptive, oncologist-reported information aimed at understanding why healthcare providers choose the treatment arm they do. In essence, the main objectives of this study were to report on trial results and, importantly, to gain insight into oncologists' treatment decisions among older patients with non-small cell lung cancer.

METHODS

Overview

The North Central Cancer Treatment Group (NCCTG) conducted these two parallel phase II trials, which were included side-by-side within the same study protocol. Institutional review boards at each specific study site within the NCCTG approved the study protocol, and all patients signed an informed consent prior to enrollment.

Enrollment criteria

Patient eligibility criteria consisted of the following: (a) histologic or cytologic diagnosis of non-small cell lung cancer; (b) unresectable cancer; (c) Eastern Cooperative Oncology Group (ECOG) performance score of 2 or better; (d) patient aged 65 years or older at the time of enrollment; (e) measurable disease, as defined by at least one lesion whose longest diameter can be accurately measured as at least 2.0 cm; (f) physician-estimated life expectancy of 12 weeks or longer; (g) patient's ability to provide written informed consent and complete questionnaires alone or with assistance; and (h) patient's willingness to participate in all translational components of the study, including blood draws and tumor block submission (results not reported here).

Patients also had to have the following laboratory parameters within 14 days of trial registration: (a) platelet count 100×10^3 cells/mL; (b) hemoglobin 10.0 g/dL; (c)

absolute neutrophil count 1.5×10^3 cells/mL; (d) total bilirubin 2.0 mg/dL; and (e) serum creatinine 2 times the upper limit of normal at the enrolling institution.

Patients were deemed ineligible in the event of any one of the following: (a) prior chemotherapy for metastatic non-small cell lung cancer; (b) concurrent radiation therapy, including palliative radiation; (c) potentially curative options such as surgery or radiation in combination with chemotherapy; (d) major surgery within 3 weeks; (e) untreated or symptomatic brain metastases (metastatic disease to the brain must have been successfully treated 2 weeks prior to initiation on chemotherapy); (f) meningeal carcinomatosis; (g) another malignancy within 5 years of trial enrollment with the exception of basal cell carcinoma of the skin; (h) active infections within 2 weeks of enrollment; (i) dysphagia or an inability to swallow intact capsules; (j) ongoing therapy with CYP3A4-inducing agents, including carbamazepine, oxcarbazepine, modafinil, ethosuximide, griseofulvin, nafcillin, phenobarbital, phenylbutazone, phenytoin, primidone, rifampin, St. John's wort, barbiturates, and sulfinpyrazone; (k) hypersensitivity to gefitinib or an excipient of this drug; (l) medical condition or laboratory parameter that would make protocol adherence difficult in the opinion of the treating oncologist; (m) grade 2 or worse peripheral neuropathy; (n) diabetes mellitus in which dexamethasone might cause complications (this criterion applied only to patients receiving chemotherapy); (o) interstitial lung disease (asymptomatic patients with chronic stable radiographic changes could be enrolled); (p) men with partners of childbearing potential unwilling to practice birth control; or (q) treatment with an investigational drug 30 days or less prior to registration.

With regard to earlier cancer treatment, patients may have had previous radiation as long as it had been completed at least 3 weeks prior to trial enrollment, all side effects had resolved, and less than 25% of the marrow cavity had been radiated. Additionally, measurable disease had to be completely outside the radiation port or there had to be a proof of progressive disease within the port region after radiation.

Baseline evaluation

A history and physical examination, including height, weight, and performance status, were to be performed on all patients within 14 days of trial registration. Baseline laboratory testing, including a hemogram, prothrombin time, serum alkaline phosphatase, aspartate aminotransferase, total bilirubin, and creatinine, was to be obtained within this same time frame. A chest radiograph and complete chest computed tomography were also to have been obtained within 14 days of registration.

Questionnaire on oncologists' treatment choice

At the time of patient enrollment, all oncologists completed a questionnaire aimed at understanding their reasons for selecting the study arm they had chosen for that particular patient. This questionnaire had been drafted by members of the study team based on clinical factors that were anticipated to be of relevance to the decision-making process. Although this questionnaire had not been previously validated, the study team undertook multiple revisions of this questionnaire in an attempt to make sure that questions were clearly written, easy to understand, and relevant to the goals of this study.

Follow-up evaluations

All patients were monitored with weekly hemograms.

A history and physical examination in addition to laboratory testing (hemogram, serum alkaline phosphatase, aspartate aminotransferase, total bilirubin, and creatinine) were performed immediately before each chemotherapy cycle. Frequent testing of the prothrombin time was advised but left to the discretion of the treating oncologist.

Tumor assessments were performed immediately prior to every other cycle of cancer therapy (chest radiograph or computerized tomographic study, as per the oncologist's discretion), and the RECIST criteria were used to assess tumor response. Cancer treatment was continued in the event of disease stability, a partial response, or a complete response. The National Cancer Institute's Common Toxicity Criteria (CTC), version 2.0, were used to assess adverse events.

Cancer treatment

On the basis of the treating oncologist's decision, patients received: (a) carboplatin and paclitaxel followed by gefitinib; or (b) gefitinib alone in a non-randomized fashion. In the first arm, patients were treated with paclitaxel 50 mg/m² intravenously on days 1, 8, and 15. Additionally, carboplatin (area under the curve = 2) was given intravenously on days 1, 8, and 15, as part of a 28-day cycle (5). This treatment was to continue for a maximum of four cycles, after which, if the patient had responsive or stable disease, then gefitinib 250 mg orally once daily, days 1–28, as part of a 28-day cycle could be prescribed. In the second arm, patients continued with gefitinib 250 mg orally once daily, days 1–28, as part of a 28-day cycle.

Dose modifications

Dosage modifications were specified in detail in the protocol. Briefly, in the first arm, myelosuppression required that paclitaxel or carboplatin either be reduced in dose or held, depending on severity. Once a dose reduction was instituted, it was to be continued for all subsequent cycles. Grade 3 neuropathy prompted a dose reduction of paclitaxel to 30 mg/m² and an omission of carboplatin. All other grade 3 or 4 non-hematologic events required that cancer treatment be permanently discontinued.

The dose of gefitinib remained fixed at 250 mg daily. However, the drug was to be held for grade 3 or 4 diarrhea; new onset of dyspnea, cough, and fever; or grade 3 or 4 rash. The drug was to be permanently discontinued in the event of drug-related interstitial pneumonitis, but otherwise treatment could be resumed once symptoms resolved or markedly improved. If treatment needed to be held beyond 14 days, then gefitinib was to be permanently stopped.

Endpoints and analyses

The primary objective of these parallel phase II studies was to assess the proportion of patients who were without cancer progression at 6 months. Each arm of the study was to be assessed and reported independently. A single arm, one-stage design with an interim analysis was used to test the hypothesis that the true cancer progression-free rate at 6 months

was at most 40% versus the alternative hypothesis that it was greater than 60%. Forty-six evaluable patients were to be enrolled on each treatment arm of the study, with an additional five patients to be enrolled to the conventional chemotherapy arm followed by gefitinib in order to ensure a 20-patient sample size that received the entire regimen. If 22 or fewer successes (patients with no cancer progression at 6 months) were observed, the treatment regimen would be considered insufficiently active for this patient population to merit further study. The trial carried 90% power to detect an effective treatment, given that the true cancer progression-free rate at 6 months was at least 60%, at a 0.10 level of significance. Secondary endpoints included tumor response rates, overall survival, median progression-free survival, and adverse events. Additionally, oncologists completed a questionnaire that explored why they had selected the treatment arm they chose for each patient. These questionnaire data are presented descriptively.

It should be noted that it was never the intention of this study to compare treatment arms in view of the small sample size and the intentional, non-randomized nature of study arm assignment. Therefore, such analyses were not undertaken.

RESULTS

Demographics

Sixty-two eligible and evaluable patients were enrolled between December 2004 and February 2006. Early study closure was prompted by conflicting results from other studies on the use of gefitinib in this setting. However, of the enrolled patients, 34 received conventional chemotherapy initially, and 28 gefitinib. Three patients had been excluded from the clinical trial outcome analyses because of trial ineligibility and another because no cancer treatment was administered. These patients are nonetheless included in the oncologists' survey data. Baseline patient characteristics appeared similar between arms (Table 1).

Trial outcomes: paclitaxel and carboplatin followed by gefitinib

The patients on this arm received a median of six cycles of conventional chemotherapy (range 1–54). Only 11 of 35 patients remained on treatment long enough to receive gefitinib. The most common reason for stopping treatment early was cancer progression, which occurred in 23 patients. One patient remains on treatment at the time of this report.

With regard to the primary endpoint, 12 patients (35%) manifested no evidence of cancer progression at 6 months. Two patients manifested a partial response (6%) and 13 stable disease. There were no patients with a complete response. The median survival was 7.9 months, and the median time to cancer progression was 3.9 months (Figure 1).

This regimen was well tolerated, despite the fact that 26 patients (76%) experienced grade 3 or worse adverse events. Two patients had a grade 4 event that consisted of cerebral ischemia and pericardial effusion, although direct attribution of these more serious events to cancer treatment was not clear (Table 2).

Trial outcomes: gefitinib alone

The 28 evaluable patients on this arm received a median of five cycles of gefitinib (range 1–19). Again, the most frequent reason for stopping was cancer progression, which occurred in 22 (79%) patients.

With regard to the primary endpoint, 12 patients (35%) were without cancer progression at 6 months. One patient manifested a partial tumor response (response rate 4%) and 14 had stable disease. There were no complete responses. The median survival was 10.9 months, and the median time to cancer progression was 4.9 months (Figure 1).

Ten patients (36%) assigned to gefitinib alone experienced grade 3 or worse adverse events, all of which were non-hematologic (Table 2).

Oncologists' treatment choice

A total of 44 different oncologists completed a questionnaire. Among the 37 patients assigned to receive chemotherapy initially (three were not included in the analyses above as noted earlier), oncologists said that their most frequent reason for choosing chemotherapy upfront was their belief that the cancer was aggressive and therefore merited a more aggressive intervention such as initial chemotherapy (Table 3). In contrast, for the 28 patients who received gefitinib alone, the most commonly chosen reason for starting this treatment was that the patient did not want chemotherapy (Table 3). As many as nine patients who received gefitinib would not have received any cancer therapy had this agent not been available. Interestingly, age alone did not appear to determine who received which treatment.

DISCUSSION

This study had two main goals. The first was to assess clinical outcomes among patients who received either conventional chemotherapy followed by gefitinib or gefitinib alone, and the second was to explore what factors prompted oncologists to prescribe the treatment they did. With regard to the first goal, the percentages of patients who were without cancer progression at 6 months were 35% and 39% with these respective treatments. Although these results may be of lesser interest given gefitinib's current unavailability in the United States and the modest nature of these results, nonetheless, when coupled with the other clinical data of efficacy, these findings suggest that these two regimens carry antineoplastic activity and favorable adverse event profiles (4, 5). For the reasons cited above, however, our group is not planning further development of either of these regimens.

Secondly, and perhaps of greater interest, this study delved into what factors led to oncologists to prescribe the treatment regimen they did. The choice of a targeted agent, such as gefitinib, seems to have been heavily patient-driven in as many as 61% of patients in whom it had been prescribed. Moreover, concern on the part of oncologists that the patient required a more aggressive treatment prompted the initiation of conventional chemotherapy—perhaps in a manner analogous to how patients can respond more slowly to hormonal therapy. The intention of this study was not to compare clinical outcomes between study arms, but it might appear ironic that clinical outcomes appeared more favorable in gefitinib-

treated patients, despite oncologists' describing the importance of upfront chemotherapy for aggressive tumors. These findings are also very much in keeping with the findings from Mok *et al.*, who, in a very select population, observed better comparative outcomes with single-agent gefitinib as opposed to a combination of carboplatin and paclitaxel (6). Overall, however, this study found that choice of therapy is complex and not driven by age alone.

Finally, it should be noted that this study carries limitations. Specifically, there had been no molecular testing of tumors for epidermal growth factor receptor mutations to direct therapy, and, as alluded to, gefitinib is no longer readily available in the United States. Despite such limitations, our findings provide preliminary insight into how oncologists make treatment decisions in elderly cancer patients. The importance of understanding such decision-making becomes particularly relevant in the context of a growing population of elderly lung cancer patients.

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Figure 1.
Time to cancer progression and overall survival in patients who received gefitinib and who received chemotherapy followed by gefitinib.

Table 1Baseline demographics^a

	Patients receiving chemotherapy followed by gefitinib (<i>N</i> = 34), <i>n</i> (%)	Gefitinib alone-treated patients (<i>N</i> = 28), <i>n</i> (%)	<i>p</i> value
Age, median (range)	75 (65–89)	80 (65–91)	0.12
Gender			
Female	14 (41)	12 (43)	1.00
Male	20 (59)	16 (57)	
Performance score			0.34
0	9 (26)	8 (29)	
1	23 (68)	15 (54)	
2	2 (6)	5 (18)	
Cancer stage			
IIIB	7 (21)	5 (18)	0.17
IV	27 (79)	20 (71)	
Other ^b	0	3 (11)	

^aAll numbers in parentheses refer to percentages unless otherwise noted.^bIncludes patients with unresectable stage IB cancer (*n* = 1) and stage IIIA cancer (*n* = 2).

Table 2

Most common adverse events

Adverse Event ^a	Arm ^b	Grade, N (%)			
		1	2	3	4
Fatigue	Gefitinib	11 (39)	8 (29)	3 (11)	0
	Chemotherapy	11 (32)	15 (44)	8 (24)	0
Cough	Gefitinib	13 (46)	2 (7)	0	0
	Chemotherapy	20 (59)	3 (9)	0	0
Anemia	Gefitinib	0	2 (7)	0	0
	Chemotherapy	19 (56)	12 (35)	0	0
Dyspnea	Gefitinib	0	10 (36)	1 (4)	0
	Chemotherapy	0	15 (44)	5 (15)	0
Rash/Desquamation	Gefitinib	12 (43)	5 (18)	2 (7)	0
	Chemotherapy	3 (9)	5 (15)	2 (6)	0
Leukopenia	Gefitinib	0	0	0	0
	Chemotherapy	10 (29)	10 (29)	2 (6)	0
Neutropenia	Gefitinib	0	0	0	0
	Chemotherapy	6 (18)	10 (29)	4 (12)	0
Thrombocytopenia	Gefitinib	0	0	0	0
	Chemotherapy	14 (41)	0	0	0
Infection	Gefitinib	0	4 (14)	1 (4)	0
	Chemotherapy	0	5 (15)	1 (3)	0
Sensory neuropathy	Gefitinib	2 (7)	0	1 (4)	0
	Chemotherapy	8 (24)	0	0	0
Anorexia	Gefitinib	0	4 (14)	0	0
	Chemotherapy	0	5 (15)	1 (3)	0
Motor neuropathy	Gefitinib	1 (4)	0	1 (4)	0
	Chemotherapy	3 (9)	1 (3)	0	0

^aMaximum adverse events per patient.

^b“Chemotherapy” refers to paclitaxel and carboplatin followed by gefitinib, as described in the body of the paper.

Table 3Survey of oncologists' treatment choice; *n* (%)

Statement	Arm	Yes	No	No opinion
"He/she was too sick to get chemotherapy."	Gefitinib	13 (46)	14 (50)	1 (4)
"Chemotherapy has too many side effects."		15 (54)	7 (25)	6 (21)
"I cannot explain why I picked ZD1839 alone."		2 (7)	24 (86)	2 (7)
"I did not think this cancer was aggressive enough to warrant chemotherapy."		3(11)	24 (86)	1 (4)
"I thought the lab portion of the trial was important."		11 (39)	9 (32)	8 (29)
"The patient did not want chemotherapy."		17 (61)	7 (25)	4 (14)
"The patient asked for 'Iressa.'"		5 (18)	23 (82)	0
"Weekly, intravenous chemotherapy was too much of a hassle."		4 (14)	23 (82)	1 (4)
"I think ZD1839 is a great drug for lung cancer."		4 (14)	14 (50)	10 (36)
"If ZD1839 was not available, I would not treat this patient."	Chemotherapy followed by gefitinib	9 (32)	18 (64)	1 (4)
"He/she was too sick to get ZD1839 alone." ^a		6 (16)	31(84)	0
"This patient would not do well with ZD1839 alone."		15 (41)	13 (35)	9 (24)
"I thought this cancer was too aggressive to warrant just ZD1839."		26 (70)	9 (24)	2 (5)
"I did not like the lab portion of the trial."		0	20 (54)	17 (46)
"The patient asked for more aggressive treatment."		12 (32)	21 (57)	4 (11)
"The patient wanted chemotherapy."		14 (38)	13 (35)	10 (27)
"I prefer chemotherapy."		25 (68)	6 (16)	6 (16)
"I chose ZD1839 because it would be less expensive for the patient (based on their insurance coverage)."		1 (3)	23 (62)	13 (35)

^aFurther choices included due to heavy tumor burden (3), weight loss/heavy tumor burden (1), performance score/weight loss/heavy tumor burden (1), and age/performance score/weight loss/heavy tumor burden (0).