A phase II study of cetuximab and radiation in elderly and/or poor performance status patients with locally advanced non-small-cell lung cancer (N0422)

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Background: Non-small-cell lung cancer (NSCLC) is a disease of the elderly. Seeking a tolerable but effective regimen, we tested cetuximab + radiation in elderly and/or poor performance status patients with locally advanced NSCLC.

Patients and methods: Older patients [≥65 years with an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2] or younger patients (performance status of 2) received cetuximab 400 mg/m² i.v. on day 1 followed by weekly cetuximab 250 mg/m² i.v. with concomitant radiation of 6000 cGy in 30 fractions. The primary end point was the percentage who lived 11+ months.

Results: This 57-patient cohort had a median age (range) of 77 years (60–87), and 12 (21%) had a performance status of 2. Forty of 57 (70%) lived 11+ months, thus exceeding the anticipated survival rate of 50%. The median survival was 15.1 months [95% confidence interval (CI) 13.1–19.3 months], and the median time to cancer progression was 7.2 months (95% CI 5.8–8.6 months). No treatment-related deaths occurred, but 31 patients experienced grade 3+ adverse events, most commonly fatigue, anorexia, dyspnea, rash, and dysphagia, each of which occurred in <10% of patients.

Conclusion: This combination merits further study in this group of patients.

Key words: cetuximab, elderly, lung cancer, poor performance status, radiation

introduction

Non-small-cell lung cancer (NSCLC) is a malignancy of the elderly; currently, the median age of patients diagnosed with this disease is 70 years [1]. This age-based shift in incidence has spawned therapeutic challenges. Previous studies in patients with locally advanced NSCLC indicate that older patients manifest higher rates of severe adverse events compared with their younger counterparts. In a secondary analysis of a 246-patient North Central Cancer Treatment Group (NCCTG) study that tested concomitant etoposide, cisplatin, and radiation for locally advanced NSCLC, elderly patients manifested higher rates of grade 4 myelosuppression (81% versus 62%; P = 0.003) and higher rates of grade 4 pneumonitis (6% versus 1%; P = 0.02) [2]. It should be noted, however, that these analyses focused on a trial that had been designed for younger patients and that in all likelihood, relatively fit elderly patients had been enrolled. Trials specifically designed for elderly patients capture a much older cohort of patients who are likely to be at greater risk for treatment-related toxicity [3]. Thus, there remains an unmet need to devise treatment regimens that enable elderly patients to receive safe and effective cancer therapy.

In this setting, the phase II study reported here was designed to explore the role of cetuximab in elderly and/or poor performance score patients with locally advanced NSCLC. This study focused on patients who were not candidates for conventional concomitant chemotherapy and radiation, a therapeutic strategy associated with a challenging adverse event profile even in relatively healthy patients. The current study is built upon previous results that showed that cetuximab carries antineoplastic activity in patients with NSCLC, that subgroups of select elderly patients appear to benefit from the addition of chemotherapy to radiation, and that, in head and neck cancer patients, the addition of cetuximab to radiation yielded improved survival and local control compared with radiation alone [4–6].

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patients and methods

overview
This phase II study was conducted within the NCCTG, a national cooperative group funded in part by the National Cancer Institute. The institutional review boards at each individual treatment site approved the protocol before patient enrollment. All patients provided written informed consent before enrollment.

eligibility
The criteria that enabled patients to enter this trial included the following: (i) either age 265 years in conjunction with an Eastern Cooperative Oncology Group (ECOG) performance status of zero, one or two or, alternatively, age <65 years and >218 years but with a performance status of two; (ii) histologic or cytologic evidence of NSCLC; (iii) stage IIIA or IIIB NSCLC without a pleural effusion (biopsy-proven evidence of mediastinal lymph node involvement was strongly encouraged); (iv) candidate for curative radiation in the opinion of a radiation oncologist (consultation was required with a radiation oncologist who agreed that the patient could be safely irradiated per study guidelines before registration); (v) able to provide informed consent; (vi) life expectancy ≥12 weeks; and (vii) forced expiratory volume 1 (FEV1) ≥1 L.

In addition, patients had to have had the following laboratory parameters obtained within 2 weeks of study registration: (i) absolute neutrophil count of ≥1.5 × 10^9 cells/l; (ii) platelet count of ≥100 × 10^9 cells/l; (iii) hemoglobin ≥9 g/dl; (iv) total bilirubin <2 times the institutional upper limit of normal; (v) aspartate aminotransferase ≤5 times the institutional upper limit of normal; (vi) serum creatinine ≤1.5 times the institutional upper limit of normal; and (vii) magnesium greater than the institutional lower limit of normal.

In addition, any one of the following criteria made a patient ineligible: (i) pregnancy, nursing, or, if of child-bearing potential, unwilling to employ adequate contraception; (ii) uncontrolled infection; (iii) prior therapeutic radiation; (iv) prior chemotherapy for the current diagnosis of NSCLC; (v) prior treatment with an epidermal growth factor receptor inhibitor; (vi) surgical lung cancer treatment available and feasible; (vii) stage IV NSCLC, as demonstrated after a complete metastatic work-up with imaging of the brain, liver, adrenal glands, and bones; (viii) any severe underlying disease, including a psychiatric illness, that, in the judgment of the treating physician, would make the patient an inappropriate clinical trial candidate; (ix) a prior noncutaneous invasive malignancy in the preceding 5 years; (x) candidate for concomitant chemotherapy and radiation; or (xi) idiopathic pulmonary fibrosis.

pretreatment evaluation
All patients underwent a history and physical examination before starting study treatment. They were also evaluated by a radiation oncologist.

Mandatory testing included computed tomography of the chest, as well as other testing to exclude widespread metastatic disease, as alluded to above. Patients also were to have undergone a hemogram 14 days before study entry as well as other tests that included a total bilirubin, aspartate aminotransferase, magnesium and serum creatinine. Patients were to have had baseline pulmonary function tests that demonstrated a FEV1 of >1 L.

cetuximab therapy and dose reductions
Patients were treated with cetuximab 400 mg/m² given i.v. over 2 h on day 1. If well tolerated, they were subsequently treated with cetuximab 250 mg/m² given i.v. over 1 h on days 8, 15, 22, 29, 36, and 43. The protocol specified that patients be premedicated with diphenhydramine at a dose of 30 mg i.v. before the first dose of cetuximab with subsequent premedication at the discretion of the treating oncologist.

The protocol specified cetuximab dose modifications. For any allergic reaction of grade 1 or 2, patients were to have the cetuximab infusion rate slowed, and they were then to be monitored closely. For grades 3 or 4 allergic hypersensitivity reactions, the cetuximab was to be stopped immediately, and patients were to receive no further drug.

Other cetuximab-related adverse events that prompted dose modifications included a grade 3 rash which was to be treated by holding the drug for 1–2 weeks and restarting only if the rash diminished to less than a grade 2. If the rash recurred, the dose of cetuximab was to be dropped to 200 mg/m² and if there was absolutely no rash improvement, the cetuximab was to be discontinued. If the rash recurred yet a second time, cetuximab was to be decreased to 150 mg/m² and if the rash did not improve, the cetuximab was to be discontinued. Then, after a third rash recurrence, cetuximab was to be completely discontinued. Patients were advised to use palliative therapy such as antibiotics or skin moisturizers.

The protocol outlined very similar criteria for nail changes.

In contrast, any upper respiratory complication attributed to cetuximab prompted holding the drug. If interstitial lung disease was discovered, cetuximab was to be permanently discontinued. Similarly, any other grade 3 non-hematologic adverse events attributable to cetuximab was to prompt a dose reduction to 200 mg/m² the first time, then 150 mg/m² the second time. The cetuximab was always to be held for up to 3 weeks until the adverse event dropped to a grade 2 or less. For any grade 4 non-hematologic adverse event, cetuximab was to be completely discontinued.

radiation therapy and dose reductions
Conventionally fractionated thoracic radiation was to be given concomitantly with weekly cetuximab. Each patient was to receive a total radiation dose of 6000 cGy given in 30 daily fractions of 200 cGy. Radiation was to be initiated with anterior posterior/posterior anterior fields which included all gross disease (both the primary tumor and adenopathy that included nodes with a short diameter of >1 cm). Additionally, elective nodal radiotherapy was delivered to the adjacent ipsilateral hilar and mediastinal nodes until a maximum of 4400 cGy was administered to the isocenter. The block edge was to be placed 1.5–2.0 cm from gross disease and at least 3 cm below the carina. The supravacularar nodes were included in the radiation field when involved or were treated electively at the discretion of the treating physician. Then, off-cord post-oblique fields were used to boost disease to a total of 6000 cGy. The maximum dose to the spinal cord was not to exceed 4800 cGy. Patients were excluded from participation if the volume of lung receiving >2000 cGy (V20) exceeded 40%. After radiotherapy, all radiotherapy plans and ports were reviewed by two NCCTG radiation oncologists and a physicist from the Radiologic Physics Center for compliance with protocol guidelines.

Any adverse event that required hospitalization was to result in the suspension of radiation until the patient was discharged from the hospital. Radiation was also to be held for any grade 4 adverse event until the grade dropped to 3 or less. If the treating physician was absolutely certain that an adverse event that required hospitalization was not related to the radiation and did not think that the radiation would compromise recovery, then radiation could proceed while the patient was hospitalized.

follow-up evaluations
During the concomitant cetuximab and radiation therapy, patients were evaluated once a week with a history and physical examination and assessment of ECOG performance status. Adverse events were also assessed and recorded on a weekly basis by means of the Common Terminology Criteria for Adverse Events, version 3 (http://ctep.cancer.gov). Patients also had a weekly hemogram, total bilirubin, aspartate transaminase, magnesium, and creatinine.

After completion of therapy, patients were assessed at 1 week with a history and physical examination and hemogram. Then, at 1 and 4 months, patients underwent a history and physical examination as well as a computerized tomographic scan of the chest that included imaging of the
adrenal glands and liver. Thereafter, at 3-month intervals, patients were evaluated with a history and physical examination and a chest radiograph. Adverse events were also assessed during all these assessments.

**statistics**

The primary end point was the 11-month survival rate [7]. A one-stage III outcome design was used in this study, which had 84% power to detect an 11-month survival rate of 65% to the 0.08 level of significance [8]. The following decision rules were formulated *a priori*. If ≥21 of the first 30 assessable patients lived to at least 6 months, the study would proceed to full accrual of 55 patients. If ≥33 of these 55 assessable patients lived for ≥11 months, this treatment regimen would be deemed promising. If 31 of 32 patients reached the 11-month point, other factors such as regimen toxicity would come into play in deciding whether further testing of this regimen would be indicated. Finally, if ≤30 of the first 55 assessable patients reached the 11-month point, this regimen would not warrant further study.

Secondary end points included adverse events, confirmed tumor response rate, time to cancer progression, and overall survival.

**results**

**demographics**

A total of 58 patients were enrolled on to this trial from May 2006 to January 2008. One patient was later found to be ineligible; this patient is not included in the efficacy analyses, but adverse event data are reported.

Baseline patient characteristics are summarized in Table 1. It should be noted that 60% of the cohort consisted of men and that the median age was 77 years (range 60–87 years). Thirty-three patients (57%) had an ECOG performance status of one, and 12 (21%) had a performance status of two. Forty-eight patients were ≥70 years of age, and 54 were ≥65 years of age. Among patients who were ≥65 years of age, eight had a performance status of two. Other baseline characteristics are shown in Table 1.

**treatment administration**

Fifty patients (86%) completed the entire 7 weeks of therapy, and five (9%) stopped early because of adverse events. One patient (2%) stopped early because of cancer progression; two chose not to receive further cancer therapy.

Half the cohort received all the weekly cetuximab treatments at full dose. The median total dose of radiation administered was 60 cGy (range 18–67.5 cGy). Twenty-two patients had interruptions in radiation for reasons that, in the majority of instances, were unspecified but in other instances included skin toxicity, severe dysphagia, technical problems with administering the radiation, and social issues.

**survival, time to cancer progression, and tumor response**

The median follow-up for this cohort was 16.9 months, and 21 patients remain alive at the time of this report. Forty of 57 patients (70%) reached the 11-month survival primary point. Although this observation indicates that cetuximab merits further study in this setting on the basis of our *a priori* set of decision rules, 48 patients (84%) have shown evidence of cancer progression at the time of this report.

The median survival for the cohort was 15.1 months [95% confidence interval (CI) 13.1–19.3 months], and the median time to cancer progression was 7.2 months (95% CI 5.8–8.6 months) (Figures 1 and 2). Moreover, 15 patients manifested a partial response, and none manifested a complete response, thereby yielding a total confirmed response rate of 26% (95% CI 16% to 40%) as per RECIST criteria [9].

**adverse events**

As stated earlier, adverse event data pertain to all patients who received any treatment on study, including the one ineligible patient. There were no treatment-related deaths. However, 31 patients experienced at least one grade 3 or worse adverse event. Similarly, five patients suffered at least one grade 4 adverse event. The most common severe adverse events were fatigue which occurred in 9% of patients, loss of appetite which occurred in 9%, shortness of breath which occurred in 9%, rash which occurred in 7%, and dysphagia which occurred in 7% (Table 2).

**Table 1.** Baseline characteristics

<table>
<thead>
<tr>
<th>Age, years</th>
<th>77 (60–87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>0 (13 (22))</td>
</tr>
<tr>
<td>1</td>
<td>33 (57)</td>
</tr>
<tr>
<td>2</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female 23 (40)</td>
</tr>
<tr>
<td>Male</td>
<td>35 (60)</td>
</tr>
<tr>
<td>Stage</td>
<td>IIA 34 (59)</td>
</tr>
<tr>
<td>IIB</td>
<td>24 (41)</td>
</tr>
<tr>
<td>Tumor histology</td>
<td>Adenocarcinoma 22 (38)</td>
</tr>
<tr>
<td>Squamous</td>
<td>25 (43)</td>
</tr>
<tr>
<td>Other or unspecified</td>
<td>11 (19)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses refer to percentages unless otherwise specified.

**Figure 1.** The median survival for this 57-patient evaluable cohort was 15.1 months (95% confidence interval 13.1–19.3 months).
This 57-patient trial tested cetuximab in combination with radiation in elderly and poor performance status patients with locally advanced NSCLC. On the basis of the fact that >50% of patients lived beyond the anticipated 11-month mark and that the adverse event profile appeared acceptable, this regimen appears promising and merits further evaluation in this group of patients. Indeed, the median survival for this 57-patient cohort was 15.1 months, an interval that exceeds that observed in the seminal age-unspecified study from Dillman et al. [7] in which patients lived a median of 9.6 and 13.7 months with radiation alone and with concomitant cisplatin-based chemotherapy and radiation, respectively. On the basis of these benchmark data, the current study indicates that cetuximab and radiation may be of greater value to patients than radiation alone and perhaps may even rival standard cisplatinum-based chemotherapy in combination with radiation. Thus, cetuximab in combination with radiation should be further studied in elderly and poor performance status patients who have locally advanced NSCLC and who are not acceptable candidates for concomitant conventional chemotherapy and radiation.

Is this potential survival advantage plausible? On the basis of earlier studies that have tested cetuximab in patients with NSCLC, we think it is. The Radiation Therapy Oncology Group (RTOG) recently reported on an 87-patient age-unspecified trial that treated patients with locally advanced NSCLC with a combination of cetuximab and chemoradiation [10]. Their cohort manifested a relatively favorable median survival of 22.7 months, even better than that observed in the study from Dillman et al. and even better than the results reported here. These results from the RTOG are in alignment with the results reported here. Admittedly, the evolution of chemotherapy since the study from Dillman et al. and the fact that the current study did not capture data on later-line therapy makes it impossible to conclude for sure that other factors extraneous to the study intervention (such as later-line therapy) were not contributing to these improved survival rates. Nonetheless, the results of the current trial, coupled with earlier results from the RTOG, indicate that further study of this combination of cetuximab and radiation is warranted in elderly and/or poor performance status patients with this malignancy.

Finally, a unique aspect of the current study is its focus on elderly patients with NSCLC. Not only has this malignancy and others become diseases of the elderly, as alluded to earlier, but, to our knowledge, next-to-no studies report an absence of ageism in the provision of cancer care. Having recently reviewed this topic, Kagan [11] describes how ageism manifests as less cancer treatment, less clinical trial enrollment, less social support, and, of course, poorer outcomes for the elderly. Hence, the continued study of cetuximab and radiation in the elderly appears not only feasible but also timely.

### Table 2. Select grade 3 and 4 adverse events of any attribution ($N=58$)

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Rash</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal hemorrhage</td>
<td>0</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

*Percentages refer to the number of patients within the entire cohort.

### discussion

This 57-patient trial tested cetuximab in combination with radiation in elderly and poor performance status patients with locally advanced NSCLC. On the basis of the fact that >50% of patients lived beyond the anticipated 11-month mark and that the adverse event profile appeared acceptable, this regimen appears promising and merits further evaluation in this group of patients. Indeed, the median survival for this 57-patient cohort was 15.1 months, an interval that exceeds that observed in the seminal age-unspecified study from Dillman et al. [7] in which patients lived a median of 9.6 and 13.7 months with radiation alone and with concomitant cisplatin-based chemotherapy and radiation, respectively. On the basis of these benchmark data, the current study indicates that cetuximab and radiation may be of greater value to patients than radiation alone and perhaps may even rival standard cisplatinum-based chemotherapy in combination with radiation. Thus, cetuximab in combination with radiation should be further studied in elderly and poor performance status patients who have locally advanced NSCLC and who are not acceptable candidates for concomitant conventional chemotherapy and radiation.

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**disclosure**

The authors have no conflicts of interest.

**references**


