Carboplatin/Paclitaxel or Carboplatin/Vinorelbine Followed by Accelerated Hyperfractionated Conformal Radiation Therapy: A Preliminary Report of a Phase I Dose Escalation Trial from the Carolina Conformal Therapy Consortium


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Key Words. Carboplatin · Paclitaxel · Vinorelbine · AHCRT · TRT

ABSTRACT

The maximum tolerated dose of conformal radiation therapy delivered at 1.6 Gy bid is being assessed in patients with unresectable stage IIB-IIIB non-small cell lung cancer who have been treated with induction regimens consisting of carboplatin plus paclitaxel or carboplatin plus vinorelbine. Data from the early stages of this parallel phase I study show that the two induction regimens are similar in toxicity and that both induce partial responses in 45% of patients. Both regimens can be followed by conformal radiotherapy using an accelerated hyperfractionated schedule to a dose of at least 80 Gy without experiencing unacceptable toxicity. Key morbidity observed thus far has involved the esophagus. Further cohorts of patients will receive higher doses of conformal radiotherapy (in 6.4 Gy increments) until the maximum tolerated dose is reached.

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INTRODUCTION

Conventional doses of thoracic radiation therapy (TRT) (i.e., 60-66 Gy) have been ineffective at sterilizing local tumor in patients with unresectable stage III non-small cell lung cancer (NSCLC) [1-4]. Attempts at dose escalation of TRT have been limited because of toxicity issues when higher doses are used. Using conformal planning techniques, it is possible to increase the radiation dose administered, perhaps by improving tumor targeting and limiting excessive dose to normal tissue [5]. Other strategies with fractionated accelerated schedules may also lead to improved local efficacy of TRT. In a trial in which 49 patients received TRT therapy alone, a novel concurrent boost technique (in which treatment was administered at 1.6 Gy bid) enabled a total radiation dose of 73.6 Gy to be delivered without incurring unacceptable toxicity [6]. In this study, the median survival was 15.3 months. The two-year survival rate of 46% was also promising, and 64% of these patients were free from local progression at two years.

Occult systemic involvement is often present at the time of diagnosis in the form of micrometastases in patients with unresectable stage III NSCLC [7-10]. The rationale for the use of induction chemotherapy in stage IIIA/IIIB NSCLC includes eradication of systemic micrometastases, which has been suggested by Arriagada and colleagues [11]. Several trials comparing platinum-based induction regimens followed by TRT, compared to TRT alone in unresectable stage IIIA/B disease, have reported longer median and long-term survival among patients receiving the induction chemotherapy [3, 12-14]. Unfortunately both local and distant control remains suboptimal, and novel
approaches addressing strategies designed to improve both local and distant control are needed [3, 5, 12-14].

The trial (C-3DRC 9701) presented in this paper was undertaken to address these issues. The primary purpose of the study was to incorporate conformal planning techniques in a dose-escalation trial of accelerated hyperfractionated conformal radiation therapy (AHCRT) in patients who had received one of two “modern” induction chemotherapy regimens. In essence, the design of the trial was that of two phase I studies run in parallel. The induction chemotherapy regimens consisted of paclitaxel plus carboplatin (CP) and vinorelbine plus carboplatin (CV). The reasons for the inclusion of carboplatin were based on the improved survival observed with the platinum-based induction regimens in previous randomized trials and the potential for a lower incidence of adverse events. Vinorelbine or paclitaxel combined with platinum have demonstrated appreciable activity as induction therapies, with manageable safety profiles [15-21].

OBJECTIVES

The primary objective of the trial was to determine the maximum tolerated dose (MTD) of three-dimensional AHCRT in patients with inoperable stage IIB or IIIA/B NSCLC following induction chemotherapy.

The study has several secondary objectives. First, it was intended to compare the pattern of toxicities of the two induction regimens in the context of subsequent escalating doses of AHCRT. Second, it was designed to examine the influence of AHCRT and chemotherapy regimen on survival, failure-free survival and sites of relapse. Third (although no data on this aspect of the trial are available to date), the study contains a correlative science component: toxicity (particularly lung toxicity) is to be examined in relation to serial levels of transforming growth factor-β/macrophage inflammatory protein-1 α, aspects of radiation dose and volume, and patients’ initial pulmonary function tests.

DESIGN AND METHODS

Eligible patients had a histologic or cytologic diagnosis of NSCLC and inoperable stage IIB or IIIA/B NSCLC following induction chemotherapy.

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DESIGN AND METHODS

Eligible patients had a histologic or cytologic diagnosis of NSCLC and inoperable stage IIB or stage IIIA/B disease. Patients with supravacular or contralateral hilar lymphadenopathy were excluded, as were those with malignant pleural effusion. Patients were required to have a performance status (PS) of 0-2, a forced expiratory ventilation in one second (FEV1) greater than 1L, or a predicted post-radiation FEV1 of 0.8L or greater, and adequate end-organ function.

All patients received two cycles of induction chemotherapy, followed by escalating doses of AHCRT starting on day 43 of treatment. The MTD of radiation therapy is to be determined separately for patients receiving CP and those receiving CV. At each dose level of radiation, it was intended that seven patients be accrued to each chemotherapy regimen, and dose level of AHCRT with a minimum of five patients evaluable for toxicity. Toxicity was assessed using the SOMA-LENT criteria [22].

The MTD was determined according to two criteria. The first related to the numbers of patients experiencing toxicities of a defined grade within a minimum of six weeks following the completion of radiotherapy. Thus dose escalation was stopped (and hence the MTD reached) if there were three or more cases of grade 3 toxicity, two or more cases of grade 4-5 toxicity, or two cases of grade 3 toxicity plus one case of grade 4-5 toxicity. The second stopping rule required an end to dose escalation if toxicity necessitated a dose delay in AHCRT of more than two weeks in 50% or more patients.

Chemotherapy

The treatment schema is shown in Figure 1. Two induction regimens were studied: CP and CV. Patients were enrolled in groups of 14 per radiation dose level, the first seven receiving CP and the second seven CV. At the start of the study, the doses used were: carboplatin area under the concentration time curve (AUC) = 7; paclitaxel 225 mg/m² infused over 3 h and vinorelbine 30 mg/m². Patients treated with CV were supported by 100 mg G-CSF q.d. The doses of carboplatin and vinorelbine were later reduced (see below).

Radiation Therapy

Induction chemotherapy was followed by escalating doses of conformally planned (PLUNC: Plan University of North Carolina) AHCRT. Regional lymph nodes received a minimum of 1.25 Gy bid to a total of 45 Gy. The initial cohort of patients received a total dose of 73.6 Gy. This dose was raised by 6.4 Gy for the second cohort and will then be further raised in two further stages to total doses of 86.4 Gy and 92.8 Gy (cohorts 3 and 4).

<table>
<thead>
<tr>
<th>Chemo 1: Paclitaxel + Carboplatin</th>
<th>Day 43 bid Radiotherapy</th>
<th>Chemo 2: Vinorelbine + Carboplatin</th>
<th>Day 43 G-CSF 100 µg/q.d.</th>
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<tbody>
<tr>
<td>X 2 cycles</td>
<td>Dose Escalation</td>
<td>X 2 cycles</td>
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<tr>
<td></td>
<td>Cohort 1: 73.6 Gy</td>
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<td></td>
<td>Cohort 2: 80.0 Gy</td>
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<td></td>
<td>Cohort 3: 86.4 Gy</td>
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<td>dl, 8, 15</td>
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<td>Cohort 4: 92.8 Gy</td>
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Carboplatin AUC 7 \rightarrow AUC 6 beginning CV 80 Gy d1
Paclitaxel 225 mg/m² dl
Vinorelbine 30 mg/m² \rightarrow 20 mg/m² beginning CV 80 Gy d1, 8, 15
G-CSF 100 µg/q.d.

Figure 1. Study 9701 treatment schema.
The initial 57.6 Gy (in 36 fractions) were given using the concurrent boost technique (1.25 Gy bid to the clinical target volume and 1.6 Gy total to all areas of prechemotherapy gross disease). The remaining dose was delivered to the post-chemotherapy gross target volume. The normal tissue tolerances were taken as spinal cord <50 Gy, heart <40 Gy, esophagus <73.6 Gy to >6 cm, and chest wall <70 Gy.

RESULTS

Patients
The data presented here relate to the first 29 patients studied, representing the first two cohorts in the trial, i.e., those treated at AHCRT doses of 73.6 Gy and 80 Gy. Their median age was 61; 19 were male. One patient had stage IIB disease, 21 were stage IIIA and seven stage IIIB. The median tumor size was 4.5 cm and median tumor volume 71 cc. The patients’ PS was 0 in 17 cases, 1 in 11, and 2 in 1. Six patients (21%) had experienced weight loss of greater than 5%. The most common histology was squamous carcinoma (11 patients), with the remainder divided among adenocarcinoma, large cell carcinoma, and carcinoma not otherwise specified.

Treatment
In both combination chemotherapy regimens, dose adjustments were made after the first cohort of patients had been treated. Thus patients who received 80 Gy of AHCRT received a reduced dose of carboplatin, targeted to achieve an AUC of 6. Patients assigned to CV chemotherapy received a lower dose of 20 mg/m² vinorelbine without G-CSF from the second cohort onwards.

A total of 14 patients received CP induction chemotherapy and 15 received CV. Of the former, half were enrolled in the first cohort and half in the second; all seven patients in the first group and six patients in the second group were evaluable for radiation therapy MTD. Of the 15 CV patients, eight were enrolled to receive 73.6 Gy radiation and seven to receive 80 Gy. In both groups, six patients were evaluable for radiation toxicity. The four non-evaluable exhibited progressive disease and therefore did not complete AHCRT. Of the five non-evaluable patients, three progressed, one expired before radiotherapy, and one removed herself from the study.

Induction Chemotherapy: Adverse Events and Response
The toxicities associated with the two induction chemotherapy regimens were broadly similar, and primarily hematological. It should be noted that half the patients whose data contributed to Table 1 were treated with doses of carboplatin and vinorelbine which were subsequently reduced following experience with the first cohort.

The rates of response observed with the two induction regimens were similar, and the response rate in this study following two cycles of CP was similar to other published studies using this regimen (Table 1) [21].

Adverse Events Following Radiotherapy
The toxicities experienced following AHCRT in the first two cohorts of patients studied (73.6 and 80.0 Gy) have not yet met the criteria for MTD. There were no instances of grade 3 or 4 lung toxicity. The most frequent toxicity encountered was esophagitis: there was one case of grade 3 toxicity in a patient receiving CP chemotherapy plus 80 Gy radiation, one case of grade 3 toxicity among a patient receiving CV chemotherapy plus 80 Gy radiation, and one case of grade 4 toxicity in a patient receiving CV + 73.6 Gy radiation.

On the basis of these data, radiotherapy dose escalation continues in both arms of the study. Currently, patients are being treated to an AHCRT dose of 86.4 Gy.
Overall Response and Survival
Following induction chemotherapy and AHCRT, four patients (14%) have experienced a complete response and eight (28%) a partial response. In two patients, lesions show fibrosis and five (17%) have stable disease. Median and one-year survival for the entire group of 29 patients is 16.2 months and 65%, respectively.

DISCUSSION
This study, which is still in progress, provides data suggesting that either paclitaxel or vinorelbine can be used in combination with carboplatin in induction chemotherapy for patients who will subsequently be treated with AHCRT. The 29 patients for whom data are available at this stage are representative of the wider population of patients with unresectable stage IIB/IIIB NSCLC.

The exciting aspect of this trial involved the novel radiotherapy strategy which utilizes conformal planning techniques to escalate the total dose of radiation delivered in this disease setting. Our preliminary data suggest that dose escalation of AHCRT on this schedule is possible at least to 80 Gy with acceptable levels of toxicity. Accrual continues in a phase I fashion to determine the MTD of AHCRT following induction CP and CV.

ACKNOWLEDGEMENT
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