Induction Chemotherapy Followed by Concomitant Chemoradiotherapy for Non-Small Cell Lung Cancer

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ABSTRACT
Multiple concepts of combined modality therapy for locoregionally advanced inoperable non-small cell lung cancer have been investigated. These include induction chemotherapy, concomitant chemoradiotherapy, and intensified radiation therapy schedules. To date, induction chemotherapy has been validated in randomized prospective trials versus radiotherapy alone. Concomitant chemoradiotherapy has led to promising results when combination chemotherapy regimens were used in the phase II setting. In addition, concomitant chemoradiotherapy has been shown to be superior to induction chemotherapy in direct comparison. Finally, accelerated radiotherapy has been shown to lead to improved locoregional control and survival in one randomized study. Based on these observations, the Cancer and Leukemia Group B (CALGB study 9431) investigated the addition of either vinorelbine, paclitaxel, or gemcitabine to cisplatin. In this trial, patients with locally advanced and inoperable non-small cell lung cancer received two cycles of induction chemotherapy with an additional two cycles of concomitant chemoradiotherapy utilizing the same agents accompanied by standard radiation to a total dose of 66 Gy. One hundred eighty-seven patients were entered on this study. An early analysis showed the median survival time was 17 months for all patients entered on the trial. In the context of other CALGB studies, the data from this trial are encouraging, and the regimens used warrant further study. The Oncologist 2001;6(suppl 1):25-27

INTRODUCTION
Recent years have seen several new approaches to the combined modality treatment of locoregionally advanced, inoperable non-small cell lung cancer (NSCLC). These approaches include induction chemotherapy, concomitant chemoradiotherapy, and intensified schedules of radiation therapy.

Induction chemotherapy has been compared with radiotherapy alone in randomized prospective trials and has been shown to improve survival [1-5]. Concomitant chemoradiotherapy achieved promising results when combination drug regimens were used in the phase II setting, and has been shown to be superior to induction chemotherapy by direct comparison [6-8]. Accelerated radiotherapy has demonstrated superior locoregional control and survival in one randomized comparison versus radiation alone [9].

The Cancer and Leukemia Group B (CALGB) study 9431 combined induction chemotherapy and concurrent chemoradiotherapy, in the hope that patients with NSCLC may be better served by receiving both approaches to treatment rather than either one alone [10, 11].

In an early CALGB trial, patients were randomized to receive either two cycles of cisplatin plus vinblastine followed by standard radiotherapy, or standard radiotherapy plus weekly doses of 100 mg/m² carboplatin. The median survival in both arms of the study was 13 months [10]. However, patients who received carboplatin as a radiation sensitizer showed a trend towards improved local and regional control.

By 1994, it was clear that several new cytotoxic agents were active in stage IV NSCLC, both when given individually and administered in combination [12-22]. It was argued that these agents should be investigated in stage III disease, and that both induction and concomitant were attractive models.

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DESIGN
With the results of that trial as background, CALGB 9431 was designed as a phase II study to determine the feasibility and activity of the sequential use of induction chemotherapy and concurrent chemoradiotherapy [11]. Eligible patients were those with Stage IIIA or B (not pleural effusion) disease and performance status 0-1. Since several potentially useful agents were available, the study had three arms. Each involved a different combination of drugs (standard cisplatin plus either vinorelbine, paclitaxel, or gemcitabine) administered for two cycles. All patients then received two cycles of concurrent chemoradiotherapy using the same agents administered during the induction phase, but at lower doses.

The endpoints of the study were the response rate in both the induction and concurrent chemoradiotherapy phases of the trial, survival, pattern of failure, and toxicity. The longer-term purpose of the study was to identify the most promising regimen to use in a phase III trial.

The regimens chosen for the induction phase were based on the experience in patients with stage IV disease [12-22]. Patients were randomized to receive 80 mg/m² cisplatin (days 1, 22, 43, 64) plus either 1,250 mg/m² gemcitabine (days 1, 8, 22, 29), or 225 mg/m² over 3 h paclitaxel (days 1 and 22), or 25 mg/m² vinorelbine (days 1, 8, 15, 22, 29) [11].

Choice of dose and schedule for the concurrent chemoradiotherapy phase was more difficult. The 80 mg/m² dose of cisplatin used was the same as that in the induction phase. However, the appropriate dose for the other agents had not been clearly established. At the stage of trial design, no formal phase I study had determined the optimal dose of gemcitabine for use with concurrent radiotherapy. However, there were data to suggest that the full 1000 mg/m² dose was not feasible in combination with large volume radiotherapy [14]. For this reason the dose chosen for the CALGB study was 600 mg/m² given on two of three consecutive weeks. The doses of 135 mg/m² paclitaxel and 15 mg/m² vinorelbine were based on published experience [14, 23]. Thus in the chemoradiotherapy phase of the study, the chemotherapy consisted of 80 mg/m² cisplatin (days 43 and 64) plus either 600 mg/m² gemcitabine (days 43, 50, 64, 71), or 135 mg/m² over 3 h paclitaxel (days 43 and 64), or 15 mg/m² vinorelbine (days 43, 50, 64, 71) [11]. Radiotherapy commenced on day 43.

RESULTS
A total of 187 patients were enrolled in the study, 180 of whom were eligible for analysis. Patient characteristics were balanced across the treatment groups for age, extent of disease and performance status. Seventy percent of patients were male and the median age was 61 years (range 30 to 81 years) [11].

ADVERSE EVENTS
In the induction phase of the study, the incidence of grade 3 or 4 granulocytopenia was 48% cisplatin and gemcitabine, 48% cisplatin and paclitaxel, and 55% cisplatin and vinorelbine [11].

During the phase of concomitant chemoradiotherapy, thrombocytopenia was frequent in patients treated with gemcitabine (53%) but virtually absent with paclitaxel (6%) and vinorelbine (0%) [11]. The incidence of grade 3 or 4 granulocytopenia was 48% with the paclitaxel combination, 51% with gemcitabine, and 27% when cisplatin was combined with vinorelbine [11]. The data on esophagitis also reflect a possible difference between regimens in the spectrum of toxicity. Incidence of grade 3 or 4 esophagitis toxicity was experienced by 50% of patients in the gemcitabine arm, by 38% of patients in the paclitaxel arm, and 24% of patients in the vinorelbine arm [11].

ACTIVITY
The proportion of patients who responded, i.e., who experienced a complete or partial response or whose disease regressed following induction chemotherapy and as an overall best response, was similar across groups.

For the study population as a whole, an early analysis showed a median survival of 17 months, and a one-year survival of 66% [11].

CONCLUSIONS
This study demonstrated that two cycles of induction chemotherapy followed by radiotherapy and two additional cycles of concurrent chemotherapy were feasible for all the study arms. Neither esophagitis nor pneumonitis were dose-limiting toxicities with these treatment regimens and no other dose-limiting toxicities were observed. The early survival statistics are encouraging and may exceed the range observed with past CALGB studies.

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