Cisplatin and Etoposide Concurrent with Radiotherapy in Non-Small Cell Lung Cancer: Single Institution Experience

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Abstract

Introduction: Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Western countries. Phase III trials have demonstrated an improvement in survival with the combination of chemotherapy and radiotherapy over radiation alone for patients with a good performance status with stage III NSCLC.

Patients and Methods: This is a retrospective study of patients with unresectable NSCLC treated with radical chemoradiotherapy at Northampton Oncology Centre in the period of May 2005-December 2010.

Results: There is a statistically significant advantage in overall survival for adenocarcinoma patients over those with squamous cell carcinoma p=0.033. Median overall survival (OS) for patients with adenocarcinoma was 37 months (std. error 13.098, 95% CI 11.328-62.672) while squamous cell carcinoma OS was 13 months (std error 7.115, 95% CI 000 26.946).

Conclusion: Our survival data for concurrent chemoradiotherapy matches with the international published data. Future research is needed to define the best concurrent chemotherapy regimen as well as the role of consolidation and maintenance chemotherapy.

Key Words: Non-Small Cell Lung Cancer (NSCLC) — Cisplatin — Etoposide — Radiotherapy.

Introduction

LUNG cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Western countries. Non-small cell lung cancer (NSCLC) represents approximately 80-85% of all lung cancer and approximately one third of patients will have stage III disease at the time of diagnosis. For patients with early stage NSCLC, surgical resection remains the standard of care. Five year survival for NSCLC remains low, ranging from 24% for patients with stage IIIA to 73% for patients with stage I disease [2].

Phase III trials have demonstrated an improvement in survival with the combination of chemotherapy and radiotherapy over radiation alone for patients with a good performance status with stage III NSCLC. Combined modality therapy is the standard of care in United States [3]. However, there has been significant variability in the overall survival observed across combined modality therapy trials [4].

It is important to identify optimal regimens of combined chemotherapy and radiotherapy and to evaluate the feasibility and efficacy of such combinations 151.

The goals of these approaches are to gain control of localized disease and to eradicate distant micrometastatic disease [6]. A meta analysis of 11 randomized trials has shown that the addition of cisplatin- based chemotherapy to radiotherapy is associated with a 10% reduction in the risk of death, relative to radiotherapy alone (p=0.006). Sequential platinum-based chemotherapy followed by radiotherapy improved survival in unresectable stage III NSCLC when compared with radiotherapy alone [7]. The most notable results in this respect were reported by the Cancer and Leukaemia Group B (CALGB) [8] and the Radiation Therapy Oncology Group (RTOG) [9]. More recently, concurrent administration of chemotherapy and radiotherapy has been reported to be superior to sequential therapy by the RTOG [10] and by Japanese investigators [11,12].

However, chemoradiotherapy is also associated with significantly higher rates of grade 3 or more toxic effects [13]. As a result studies such as the phase III trial conducted by the West Japan Thoracic Oncology Group, which aimed to identify more tolerable chemotherapy regimens to be used con-
currently with thoracic radiation are of particular clinical relevance [14,15].

In this retrospective study we present Northampton Oncology Centre experience using concomitant chemoradiotherapy.

**Material and Methods**

This is a retrospective study of patients with unresectable NSCLC stages (I-III) treated at Northampton Oncology Centre in the period of May 2005-December 2010. Eligibility criteria for this study were: Cytologic or histologic diagnosis of NSCLC, stages (I-III), with the presence of measurable or assessable disease, patient age 18 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, absolute neutrophil count 2,000/mL, platelet count 100,000, hemoglobin 9.5gm/dl, serum creatinin <1.2mg/dl, forced expiratory volume in 1 second (FEV1) >800mL, and adequate liver values: Total bilirubin <1.5 times the institutional upper limits of normal (ULN), AST and ALT 2.5 times the institutional (ULN).

Patients were excluded from study participation if they had any of the following conditions: Malignant pleural effusion, distant metastases, serious medical illness or active concurrent malignancy.

Baseline assessment included a complete medical history, evaluation of PS, physical examination and assessment of vital signs, blood tests (complete blood cell count with differential and platelet counts and blood chemistry evaluation); chest radiographs and computed tomography (CT) scans of chest and upper abdomen and PET scan. Baseline evaluation had to be performed within 2 weeks before therapy initiation. All measurable lesions were identified at baseline and monitored throughout.

**Treatment plan:**

Patients started concurrent chemo-radiotherapy. The regimen used in these patients was cisplatin 50mg/m² days 1, 8, 29 and 36 and intravenous etoposide 50mg/m2 days 1 and 29 followed by oral etoposide once daily 100mg/m² on days 2-5 and 30-33 during the course of radiotherapy. Radiotherapy was delivered with photon beams generated by Linear accelerator. Administered in 2Gy/fractions/day, 5 days/week. The Gross Target Volume (GTV) included the entire tumor and involved lymph nodes on the PET scan with no elective nodal irradiation. The clinical target volume (CTV) was obtained by adding 8mm to the GTV and the PTV was generated by adding a further 7mm to CTV. Conformal radiotherapy planning was utilized to target the PTV.

**Statistical analysis:**

The primary end point of this study was the overall survival. Survival was calculated from the date of diagnosis to death or last follow-up evaluation at January 2012.

Survival curves were established with the Kaplan-meier method and were compared using the Log-rank test and Cox model. Usual statistical tests (χ² test and Fisher's exact probability test) were used to compare variables in the same treatment group. Differences were considered significant at p<0.05. These tests were run on an IBM compatible personal computer using the statistical Package for Social scientists (SPSS) for windows 10.0 (SPSS Inc., Chicago, IL, USA).

**Results**

A total of 32 patients were treated between May 2005 and December 2010. There were 23 male and 9 females. Eleven patients had PS 0 (35.5%), 16 patients (51.6%) had PS 1 while only 4 (12.9%) patients with PS 2. Most of patients (12) had adenocarcinoma (37.5%), ten patients (31.3%) had squamous cell carcinoma, three with adenosquamous and the remaining three patients had unspecified Non-Small Cell Carcinoma. (Tables 1, 2) show patient's characteristics.

Although the prescribed dose was 60-64 Gy, three patients were treated with 56Gy due to limitation of lung V20 and V5 values.

There is a statistically significant advantage in overall survival for adenocarcinoma patients over those with squamous cell carcinoma p=0.033. Median overall survival (OS) for patients with adenocarcinoma was 37 months (Std. Error 14.500, 95% CI 11.328-62.672) while squamous cell carcinoma OS was 13 months (Std. Error 7.115, 95% CI 000-26.946).

Median overall survival for patients with stage I was 37 months (Std. Error4.500, 95% CI 8.580 -65.65.420), stage II was 40 months (Std 2.449, 95% CI 35.199-44.801), stage Ma is 17 months (Std. Error 9.618 -36.184) and for stage IIb is 20 months (Std 8.792-41.208). By pair wise comparison there is statistically significant difference in overall survival for stage I versus IIb (p=0.026), stage II vs IIb (p=0.009), also better overall survival, but not statistically significant for Ma vs Mb (p=0.08).
Median overall survival for patients that were treated with radiation dose 64 Gy/32 fractions was 24 months (Std. Error 4.829, 95% CI 5.535-34.465), 60 Gy/30 fractions was 33 months (std 14.597, 95% CI 4.39-61.610) and 56 Gy/28 fractions was 13 months (std 8.981, 95% CI 0.000-30.604).

Of 32 patients, 21 patients after progression received second line chemotherapy different regimens, while 11 patients had best supportive care (34.4%). Only 6 patients received third line chemotherapy.

Toxicity:

By reviewing patients files; regarding to non-hematological toxicities, most of the patients complained of anorexia and nausea, difficult swallowing due to grade 3 esophagitis (9.3%), dry cough due to radiation pneumonitis grade 3 and 4 (6.25%). Pneumonitis and esophagitis induced have been considered serious, but they were easily manageable in the present study. For hematological toxicities, group of patients developed myelosuppresion in the form of leucopenia and neutropenia in 8 patients (25%), thrombocytopenia (12.5%), anaemia (12.5%), only one patient developed febrile neutropenia (3.1%). There was no enough data on the database to comment on the quality of life or toxicity in this patients series.

Table (1): Descriptive statistics (frequency) of different categorical risk factors.

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Table (2): Descriptive statistics.

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Discussion

Much progress has been made in recent decades in treating stage III NSCLC. Concomitant chemoradiotherapy clearly represents the current standard and the preferred approach over induction chemotherapy. There have been no phase III comparisons of different chemoradiotherapy regimens. Therefore, a specific standard regimen cannot be recommended at this time [16].

Meta-analyses of studies comparing concurrent with sequential therapy showed that there was a relative improvement of about 20% with concurrent therapy over sequential therapy in these patients and that concurrent chemoradiation is more toxic than the sequential approach, particularly with regard to oesophagitis. The incidence of pneumonitis is not significantly higher with concurrent therapy [17].

Interestingly, despite the growing popularity of second and third generation chemotherapy regimens to be used with thoracic irradiation, the National Comprehensive Cancer network (NCCN) continues to recommend cisplatin and etoposide as its preferred regimen [18].

In this retrospective study we present Northampton Oncology Centre experience using concomitant chemo radiotherapy; for 32 patients with non-small cell lung cancer, unresectable stages (I-III), received cisplatin/etoposide regimen concomitant with radiotherapy. We were one of few centers in UK who adopted the concurrent CRT in 2005 and as our center only serves less than a million, the number of eligible patients was small. Many trials have included inoperable stage I-II as our trail done.

We assessed overall survival and evaluated different risk factors. The median overall survival was 24 months. There was a significant overall survival advantage for those with adenocarcinoma over those with squamous cell carcinoma and those with stage I and II compared to stage III although the number of stage I and II patients was small. There was better overall survival with no significant difference for those receiving more than 56Gy/28.
A multicenter French study reported by Le Chevalier et al. [19] also confirmed improved survival for the chemotherapy plus radiotherapy arm compared to radiotherapy alone (3-year survival rates of 11% vs 5%, respectively) with an improved distant failure rate for chemotherapy plus radiotherapy (22% vs 46% at 1 year, respectively). Unfortunately, both treatment groups showed similarly high loco regional failure with 1-year local control rates of only 15% and 17%, illustrating the vexing problem of obtaining good loco regional control of disease in the locally advanced setting.

A Phase II study used concurrent cisplatin 20mg/m²/day plus etoposide 50mg/m²/day, from day 1 through day 5, every 4 weeks for four cycles, and radiotherapy administered to a total dose of 60 Gy for unresectable stage III non-small cell lung cancer. Response rate was 84%, including 68% complete response. With a minimum follow-up of 23 months, overall survival was 70% at 1 year, 39.7% at 2 years, and 34.7% at 3 years [20].

The most common detected toxicities by this protocol are considered amenable, manageable. Grade 3 esophagitis (9.3%), radiation pneumonitis grade 3 and 4 (6.25%), Leucopenia and neutropenia in 8 patients (25%), thrombocytopenia (12.5%), anaemia (12.5%), only one patient developed febrile neutropenia (3.1%). Which is comparable to common toxicities by using Concurrent Chemoradiotherapy with Carboplatin and Docetaxel for Stage III Non-Small-Cell Lung Cancer were grade 3/4 neutropenia (95%), grade 3 esophagitis (5%), grade 3 anorexia (30%), grade 3 febrile neutropenia (35%) and grade 5 radiation pneumonitis (5%) [21].

The role of induction chemotherapy followed by concurrent chemotherapy or concurrent chemoradiotherapy followed by consolidative chemotherapy remains investigational. Phase III Study by the Hoosier Oncology Group and U.S. Oncology 22 evaluated the results of phase II study by the Southwest Oncology Group 23 using consolidation docetaxel after cisplatin (P), etoposide (E), and radiation (XRT) resulted in a median survival time (MST) of 26 months, whether consolidation docetaxel was responsible for this improved survival. This randomized phase III trial failed to achieve the primary objective of improved survival with the addition of consolidation docetaxel after PE/XRT for this population of patients with stage III NSCLC. Despite the use of older chemotherapeutic agents (PE) and only 59.4Gy of XRT, the PE/XRT regimen in this study resulted in a median survival time superior to historic controls and a 3-year survival rate comparable with other regimens using newer chemotherapeutic agents and higher doses of XRT. Finally, they concluded that consolidation docetaxel after PE/XRT results in increased toxicities but does not further improve survival compared with PE/XRT alone in patients with stage III inoperable NSCLC [22]. Simirally, randomized phase III trial evaluated whether consolidation The Cancer and Leukaemia Group B (CALGB) Trial 39801 was designed to investigate the impact of induction chemotherapy in addition to standard chemoradiotherapy on overall survival [24]. The difference in survival was not statistically significant (p=0.3) and the median survival observed on the induction chemotherapy followed by chemoradiotherapy and the chemoradiotherapy alone arms was 14 and 12 months respectively [4]. The use of weekly low dose carboplatin and paclitaxel with concurrent radiotherapy may have compromised the efficacy of both treatment paradigms investigated in this trial. The trials have demonstrated a benefit of concurrent chemoradiotherapy over sequential chemotherapy [10,12]. However, when newer agents (e.g. Taxanes and gemcitabine) are used the chemotherapy dose must be reduced to avoid excessive toxicity. A phase III trial that compared weekly paclitaxel with concurrent TRT versus TRT alone after induction chemotherapy with carboplatin and paclitaxel demonstrated a significant improvement in time to tumor progression (p<0.001), but not overall survival in comparison to TRT alone (p=0.091) [25].

A randomized Phase III trial of combined paclitaxel, carboplatin, and radiation therapy followed by weekly paclitaxel or observation for patients with locally advanced inoperable non-small cell lung cancer (radiotherapy dose=66.6Gy in 37 fractions). Patients then randomized for either observation or maintenance (6 cycles of paclitaxel 70) a median of 5 of 6 planned cycles that was delivered in the maintenance arm. For the observation group vs. the maintenance group, the estimated 1 and 4-year survival rates were 77% vs. 66% and 38% vs. 17% (median, 26.3 months vs. 16.1 months, respectively [p=0.07]); the estimated 1 and 4-year performance-free survival (PFS) were 46% vs. 24% and 25% vs. 13% (median, 10.2 months vs. 8.2 months, respectively [p=0.04]) [26].

The novel concept of adding non cross resistant chemotherapy following the completion of concurrent chemoradiation was examined in a SWAG study. In this multi-institutional Single arm phase II study, 71 patients with unresectable stage IIIb NSCLC were treated with concurrent chemoradiation with cisplatin, etoposide and TRT followed by three cycles of docetaxel (75 to 100mg/m² given
every 3 weeks) (27). The median survival was an impressive 27 months, and the projected 3-year survival was 47%, which encouraged SWAG investigators to conduct a phase III study comparing this regimen (cisplatin, etoposide, and radiation followed by three cycles of docetaxel) with an identical regimen followed by maintenance therapy with ZD 1839 (Iressa), a specific inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase.

Yamamoto et al. [18] compared three different cytotoxic chemotherapy regimens administered during radiation treatment: Arm A (the control group) received four cycles of mitomycin (8mg/m² on day 1), vindesine (3mg/m² on days 1 and 8) and cisplatin (80mg/m² on day 1); arm B received weekly irinotecan (20mg/m²) and carboplatin (area under the plasma concentration-time curve [AUC] 2) for 6 weeks, followed by two courses of irinotecan (50mg/m² on days 1 and 8) and carboplatin (AUC 5 on day 1); and arm C received weekly paclitaxel (40mg/m²) and carboplatin (AUC 2) for 6 weeks followed by two courses of paclitaxel (200mg/m² on day 1) and carboplatin (AUC 5 on day 1). 5-year survival rates were essentially the same in all three chemotherapy arms, a difference favoring the cisplatin (control) arm was observed at 3 years (35%, 24% and 26% for arms A, B and C, respectively), but non-inferiority was not statistically achieved. It must also be recognized that the reported gains in the therapeutic ratio were quite modest.

**Conclusion:**

Our survival data for concurrent chemoradiotherapy matches with the international published data. Future research is needed to define the best concurrent chemotherapy regimen as well as the role of consolidation and maintenance chemotherapy.

**Conflict of interest:**

The authors have no financial or personal relationship that could inappropriately influence/bias this work.

**Limitations of the study:**

As it is a retrospective study, small sample number of patients and no control arm for comparison.

**References**


Cisplatin & Etoposide Concurrent with Radiotherapy


