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Phase II trial

A phase II trial of induction chemotherapy followed by continuous hyperfractionated accelerated radiotherapy in locally advanced non-small-cell lung cancer

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ABSTRACT

Background and purpose: We conducted a phase II study combining induction chemotherapy with continuous hyperfractionated accelerated radiotherapy (CHART) in locally advanced non-small-cell lung cancer (NSCLC).

Materials and methods: A total of 40 patients with stage III NSCLC were enrolled. All patients received 3 cycles of chemotherapy followed by CHART (56 Gy in 36 fractions over 12 days). The primary outcome measure was radiation toxicity. Secondary endpoints were response rate, overall survival, disease-free survival and loco-regional progression-free survival.

Results: Acute radiation toxicity was minimal and there were no significant late toxicities. The response rate after completion of chemoradiation was 65%. The median and 2-year overall survival, progression-free survival and loco-regional progression-free survivals were 15.7 months, 28%; 12.1 months, 23%; and 26.4 months, 51%, respectively.

Conclusions: Induction chemotherapy can be safely combined with CHART. The survival results are consistent with previous studies of chemotherapy followed by accelerated radiotherapy. This approach should be compared with synchronous chemoradiation to determine if it represents a less toxic alternative.

Chemoradiotherapy represents the current treatment standard for locally advanced non-small-cell lung cancer (NSCLC). Historically patients with stage III disease have been treated with radiation therapy alone but results were disappointing with median survivals of only 10 months. A series of clinical trials conducted in the 1980s confirmed that the addition of sequential platinum-based chemotherapy improved outcomes compared with radiotherapy alone, extending the median survival to 13 months [1–3]. Concomitant chemoradiation has also shown to be superior to single modality radiotherapy [4]. More recently sequential and concomitant chemoradiation have been directly compared in four trials [5–8]. They indicate a superiority for the concomitant approach, albeit at the cost of increased acute toxicity. However the optimal chemoradiation strategy remains the subject of debate since all of these studies are open to criticism. For example, patients in the concomitant arm often received additional cycles of chemotherapy whilst not all patients randomised to the sequential treatment arm actually went on to receive the radiotherapy. Furthermore the negative impact of chemotherapy-induced anaemia on radiosensitivity was not adequately addressed. Thus there remains significant interest in the sequential chemoradiation approach not least because it is less toxic, allows full dose chemotherapy to be given and is more readily integrated with dose-escalated radiotherapy protocols.

Overall treatment time (OTT) is being increasingly recognised as an important factor in the treatment of lung tumours with combined modality approaches [9,10]. Once cytotoxic therapies such as chemotherapy and radiotherapy are started, accelerated repopulation of surviving tumour cells may reduce the effectiveness of later cycles or fractions of treatment [11,12]. Induction chemotherapy when added to radiation therapy inevitably prolongs the OTT, which is likely to be deleterious to outcome. This phenomenon may explain the failure of induction chemotherapy to significantly improve local control despite producing significant disease shrinkage [1,2]. The increased proliferation of surviving tumour cells after chemotherapy could be partly addressed by using accelerated radiation regimens such as continuous hyperfractionated accelerated radiotherapy (CHART). In contrast to conventionally fractionated radiotherapy which takes approximately 45 days to deliver, CHART is completed in just 12 days. The pivotal phase III trial showed a 9% improvement in 2-year survival with CHART when compared with a higher dose delivered by conventional

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fractionation [13]. Therefore it seemed logical to combine induction chemotherapy with CHART in an attempt to improve the proven survival benefits of both these approaches. As far as we are aware, this is the first study to formally test the feasibility of this strategy. We have previously reported on the impact that tumour shrinkage with chemotherapy had on radiation treatment planning for patients entered in this study [14]. Herein we report the mature, outcome results of the trial.

Materials and methods

Forty patients were enrolled in a prospective phase II study evaluating the use of induction chemotherapy followed by CHART. Eligibility criteria comprised: histologically confirmed stage III NSCLC (no pleural effusion or supraclavicular lymph node disease), World Health Organisation performance status 0–1, weight loss < 5% within the preceding 3 months, satisfactory lung function (forced expiratory volume in 1 s >1.5 l) and suitability for treatment with chemotherapy. The protocol was approved by the Gloucestershire Research and Ethics Committee. Pre-treatment evaluation included history, physical examination, chest radiograph, fibre-optic bronchoscopy and contrast enhanced computed tomography (CT) scan of the chest and upper abdomen. In addition 2 patients had staging positron emission tomography (PET) scans and 6 had previous exploratory surgery. Further investigations to exclude metastases were performed if clinically indicated. Patient demographics, tumour characteristics and treatment parameters are shown in Table 1.

Treatment comprised 3 cycles of induction chemotherapy using mitomycin-C 8 mg/m^2, vinblastine 6 mg/m^2 (maximum 10 mg) and carboplatin. Mitomycin-C was omitted from the third cycle of treatment. Carboplatin was dosed using the Calvert equation, at an area under the concentration curve of 5. Glomerular filtration rate was determined using radiolabelled ethylenediamine tetraacetic acid (EDTA) clearance. Chemotherapy was delivered on a 3 weekly schedule. Treatment was delayed if the neutrophil count on the planned day of delivery was $<1.5 \times 10^9$/l or if the platelet count was $<100 \times 10^9$/l. Prophylactic antibiotics were used to minimise the risk of febrile neutropaenia. The protocol recommended that haemoglobin levels be maintained above 11 g/dl before starting radiation therapy.

Table 1
Demographics, tumour characteristics and treatment parameters. V_{20}, the fractional volume of the lung receiving >20 Gy. MLD, mean lung dose.

Age	Median 66 (range 47–79)
Gender	Male 25, female 15
Stage	
IIIA	9 (22.5%)
IIIB	31 (77.5%)
Histology	
Squamous cell	23 (57.5%)
Adenocarcinoma	7 (17.5%)
Unspecified	10 (25%)
Pre-chemotherapy tumour volume[a]	Median 125 cc (range 36–679)
Pre-chemotherapy RECIST measurement[a]	Median 65 mm (range 23–137)
Tumour location (lobe)[b]	
Right upper	14 (35%)
Right middle	5 (12.5%)
Right lower	4 (10%)
Left upper	9 (22.5%)
Left lower	7 (17.5%)
Tumour position[b]	
Central	32 (80%)
Peripheral	7 (17.5%)
Radiotherapy parameters	
V_{20}	Median 23% (range 4–41%)
MLD	Median 12.3 Gy (range 5.2–18.4)

[a] Pretreatment tumour volume measurement in 36 assessable patients.
[b] In one patient the site of the primary could not be defined.

CT scans for radiotherapy planning were performed before starting and 2 weeks after completion of chemotherapy. These were subsequently spatially coregistered using XiO software (Computerized Medical systems, St. Louis, MO). CHART was commenced 3.5–4 weeks after the completion of chemotherapy. Our radiotherapy protocol has previously been described in detail [14]. Briefly, all patients were treated with 3-dimensional conformal radiation therapy. The primary and involved lymph nodes were included in a single phase of treatment. Pre-chemotherapy tumour dimensions were used to form the target volume. Most patients were treated with three coplanar beams designed such that the spinal cord did not received >40 Gy and that the fractional volume of lung receiving >20 Gy (V_{20}) did not exceed 35%. Radiotherapy planning was performed with the XiO treatment planning system and its forerunners. All patients received CHART (54 Gy prescribed to the isocentre in 36 fractions over 12 days, treating three times a day with an interfraction interval of 6 h). The median OTT from the start of chemotherapy to finishing radiation therapy was 82 days (range 72–114).

Patients were monitored weekly during and following the completion of radiotherapy, either for a minimum of 6 weeks or until resolution of acute radiation toxicity. Subsequent follow-up visits were at 3 monthly intervals for life. A CXR was performed at 4 weeks and at every subsequent visit. Post-therapy CT scans were performed routinely at 3 months and 12 months after the end of treatment, then yearly. Acute toxicity to chemotherapy was recorded using the National Cancer Institute common toxicity criteria (version 2) and acute and late toxicity to radiotherapy using Radiation Therapy Oncology Group criteria.

The primary outcome measure was radiation toxicity. The secondary endpoints were response rate at 3 months, overall survival (OS), progression-free survival (PFS) and loco-regional progression-free survival (LR-PFS). The Response Evaluation Criteria in Solid Tumours (RECIST) measurement were used to determine response rates [15]. Survival was defined as the time from entry into the study to the event and was calculated using the Kaplan–Meier method. Patients who remained alive were censored as of May 2008. Treatment on progression comprised second line chemotherapy (gemcitabine or docetaxel based) in 14 and tyrosine kinase inhibitors (gefitinib or erlotinib) in 4.

The rate of tumour growth after relapse was measured on serial diagnostic scans. Tumour volumes were estimated using the formula $4/3\pi(D_{l-r}/2 \times D_{a-p}/2 \times D_{c-c}/2)$ where D_{l-r} is the maximum diameter in the left to right direction, D_{a-p} is the maximum diameter in the anterior to posterior direction and D_{c-c} is the maximum diameter in the cranio-caudal direction. The tumour volume doubling time (V_d) was calculated using the standard volumetric formula $V_d = (t \cdot \ln 2)/[\ln V_f/V_i]$ where t is the time in days between the two CT scans, V_f is the volume measured on the final CT scan and V_i is the volume measured on the initial CT scan.

Statistical analyses were performed using SPSS (SPSS Inc, Chicago, IL). Pearson's correlation coefficient Student's t-test, paired sample t-tests and chi-squared tests were used as appropriate.

Results

Chemotherapy was well tolerated and all patients completed 3 cycles of treatment as planned. Ten patients experienced a grade 3 or above chemotherapy toxicity, mostly myelosuppression (Table 2). All toxicities were transient and resolved spontaneously. The most common acute radiation complication was oesophagitis which occurred in 38 (95%) patients (Table 2). In only 1 patient was this $\geqslant$grade 3 (weight loss > 15% and/or requiring opiate analgesics/feeding support) and in all cases oesophagitis resolved with