A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1)

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Background: Phase III studies suggest that non-small-cell lung cancer (NSCLC) patients treated with cisplatin–docetaxel may have higher response rates and better survival compared with other platinum-based regimens. We report the final results of a randomised phase III study of docetaxel and carboplatin versus MIC or MVP in patients with advanced NSCLC.

Patients and methods: Patients with biopsy proven stage III–IV NSCLC not suitable for curative surgery or radiotherapy were randomised to receive four cycles of either DCb (docetaxel 75 mg/m², carboplatin AUC 6), or MIC/MVP (mitomycin 6 mg/m², ifosfamide 3 g/m² and cisplatin 50 mg/m² or mitomycin 6 mg/m², vinblastine 6 mg/m² and cisplatin 50 mg/m², respectively), 3 weekly. The primary end point was survival, secondary end points included response rates, toxicity and quality of life.

Results: The median follow-up was 17.4 months. Overall response rate was 32% for both arms (partial response = 31%, complete response = 1%); 32% of MIC/MVP and 26% of DCb patients had stable disease. One-year survival was 39% and 35% for DCb and MIC/MVP, respectively. Grade 3/4 neutropenia (74% versus 43%, P < 0.005), infection (18% versus 9%, P = 0.01) and mucositis (5% versus 1%, P = 0.02) were more common with DCb than MIC/MVP. The MIC/MVP arm had significant worsening in overall EORTC score and global health status whereas the DCb arm showed no significant change.

Conclusions: The combination of DCb had similar efficacy to MIC/MVP but quality of life was better maintained.

Key words: chemotherapy, docetaxel, lung cancer, quality of life

introduction

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related death throughout Europe and the United States and is responsible for approximately 1 million deaths worldwide each year [1]. The results of two meta-analyses showed that cisplatin-based chemotherapy was associated with a modest improvement in overall survival [2, 3]. Two large randomised trials of triple drug regimens [mitomycin, cisplatin with either ifosfamide or vinblastine (MIC or MVP)] versus best supportive care showed a survival advantage and improved quality of life (QoL) for the chemotherapy arm [4–6]. Both studies used lower doses of cisplatin, i.e. 50–60 mg/m² and included a significant proportion of patients with poor performance status. More recently, a number of newer agents have been shown to have significant activity in NSCLC [7–10]. Docetaxel was noted to have single-agent activity in NSCLC compared with best supportive care, significantly improving overall survival, clinical symptoms and QoL. The feasibility, tolerability and activity of the docetaxel/carboplatin (DCb) combination administered as an outpatient was confirmed in a number of phase I and II trials [11–13]. The combination was attractive as a convenient outpatient regimen that could be given every 3 weeks with the carboplatin dose being determined by renal function. At the time of initiation of this study, few studies had compared a newer platinum based doublet with the established older triplet regimens. We report the results of a large, randomised,
phase III trial of docetaxel/carboplatin versus MIC or MVP in patients with advanced NSCLC, with survival and QoL as the main end points.

**patients and methods**

**patient selection**

Eligible patients were required to fulfill the following criteria: pathologically confirmed inoperable NSCLC (stage III/IV), ineligible for curative radiotherapy, no prior chemotherapy or radiotherapy; Eastern Cooperative Oncology Group (ECOG) performance score of 0–2; age > 18 years with life expectancy of at least 12 weeks; adequate bone marrow reserve (neutrophils ≥ 2.0 x 10^9/l, platelets ≥ 100 x 10^9/l, haemoglobin ≥ 10 g/dl); adequate hepatic and renal function (serum creatinine ≤ 1.0 x upper limit of normal or creatinine clearance ≥ 50 ml/min). The protocol was approved by the local Research Ethics Committee and/or Institute Review Board and all patients gave written informed consent.

Disease measurement was performed within 4 weeks of the start of treatment. In seven centres, patients receiving chemotherapy were additionally evaluated for QoL using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire augmented by the LC-13, and the Hospital Anxiety and Depression (HAD) scale.

**stratification and treatment**

The study design was a randomised, multicentre, phase III comparative study of docetaxel plus carboplatin versus MIC or MVP as first-line therapy in patients with inoperable NSCLC. Patients were stratified by centre, disease stage and performance status before being randomised by the Department of Medical Statistics, Christie Hospital. Patients were randomly assigned to either DCb or the standard arm (MIC or MVP) determined prior to study start, depending on centre preference. Patients randomised to DCb received docetaxel 75 mg/m² as a 1-h infusion followed by carboplatin at a dose calculated to give an area under the curve of 6. A premedication of dexamethasone 8 mg b.i.d. orally for six doses was commenced 24 h before each cycle. MVP was administered as mitomycin C 6 mg/m² i.v. bolus, ifosfamide 3 g/m² i.v. bolus and cisplatin 50 mg/m² i.v. infusion. MIC was administered as mitomycin C 6 mg/m² i.v. bolus, ifosfamide 3 g/m² i.v. infusion with Mesna uroprotection and cisplatin 50 mg/m² i.v. infusion. Patients receiving MIC and MVP received pre- and post-hydration according to local practice. Anti-emetics were given routinely, in accordance with local practice. Chemotherapy was administered every 3 weeks to a total of four cycles. Patients receiving DCb were treated in an outpatient setting but the majority of MIC/MVP patients were admitted overnight for chemotherapy. Treatment was delayed in the event of haematological toxicity (white cell count < 3 x 10^9/l, neutrophils < 1.5 x 10^9/l, platelets < 100 x 10^9/l) until recovery or for a maximum of 2 weeks. In the docetaxel/carboplatin arm, a dose reduction in docetaxel to 60 mg/m² was allowed if grade 3–4 febrile neutropenia or infection developed. Treatment was delayed for a maximum of 3 weeks in the event of the measured creatinine clearance being ≤ 50 ml/min and patients were withdrawn from the study thereafter.

**response, survival, QoL and toxicity criteria**

Baseline and post-chemotherapy CT scanning was performed together with Chest x-ray (CXR), full blood count, biochemistry and measured creatinine clearance before each cycle of treatment.

QoL was evaluated before treatment, on day 14 of each cycle and 4 weeks and 8 weeks after the final cycle of treatment. To take into account variability in the date on which QoL was recorded, a boundary of 10 days either side of the due date during study was allowed, with the exception of the baseline forms that had to be completed within 1 week before the first treatment. Imputation of missing values and missing forms was not carried out. Longitudinal analyses, using Mann–Whitney U-tests (two-tailed) were planned to compare the AUCs of each arm up to the 8-week post-treatment point for mean change from baseline. However, due to patient attrition in both arms, analysis was confined to the four treatment cycles and did not include the follow-up period. Since small differences in scores were unlikely to reflect clinical benefit, interest was focused on those subscales or symptom items that showed a ≥ 10% between-treatment difference in the number of patients who improved or deteriorated [8].

Maximum treatment toxicity (NCI-CTC, version 2.0) for each cycle was recorded on day 14.

**statistical analysis**

The primary end point was 1-year survival. Secondary end points were 2-year survival, toxicity and QoL. Based on previous reports, the study was designed to have a 90% power to detect a 15% 1-year survival difference, from 25% to 40%, and required 432 patients [4, 13, 14]. An interim analysis by an independent data monitoring committee was planned and subsequently carried out when 264 patients had been randomised. Survival estimates were calculated using Kaplan–Meier curves and confidence intervals were calculated using Greenwood’s variance formula. QoL scores were calculated using the method laid out in EORTC QLQ-C30 Scoring Manual. Comparisons of overall scores, global health status score, HAD and LC-13 scores, within and between arms, were made using Wilcoxon and Mann–Whitney U-tests.

**results**

**patients and treatment administration**

Four hundred and thirty-three patients were recruited by 17 institutions between June 2001 and November 2002, of which 216 patients were randomised to receive MIC/MVP and 217 to receive DCb. Eleven patients were excluded from analysis (six MIC/MVP, five DCb); seven patients were ineligible (two inadequate creatinine clearance, two histology not confirmed, two inaccurate stage, one had received previous radiotherapy), one co-existing morbidity, one judged not fit at the time of CT, one withdrew consent and one whose notes were lost. Two hundred and ten patients receiving MIC/MVP and 212 patients receiving DCb were assessable for efficacy and toxicity.

In general, patient and tumour characteristics were similar and are summarised in Table 1. Ninety patients (20.7%) were performance status 2. There were fewer performance status 2 patients (18 versus 23%, P = 0.28) and stage IV (50 versus 53%, P = 0.31) in the DCb arm. Approximately 14% of patients were staged as having stage IIIA disease but were not deemed fit for surgery or radical chemoradiotherapy because of bulky nodal disease.

Sixty-four per cent of all patients completed four cycles of treatment (66% in the MIC/MVP arm and 62% in the DCb arm) with a median of four cycles in each arm and an equivalent number of dose delays in both arms. The most common cause for failure to complete four cycles of chemotherapy was disease progression.

Seven patients in the DCb arm suffered an allergic reaction to docetaxel necessitating a crossover to MIC/MVP. There was no difference between arms (MIC/MVP versus DCb) in the rate of palliative radiotherapy (33% versus 31%), radical radiotherapy (8% versus 10%) or surgical resection following completion of treatment (1.9% versus 0.9%). Additional
treatment following the recognition of progressive disease was given to 42% of patients after MIC/MVP (17% palliative radiotherapy, 10% chemotherapy and 15% other treatment) and 46% after DCb (22% palliative radiotherapy, 9% chemotherapy and 15% other treatment).

**survival and response**

With a median follow-up of 17.4 months there was no significant difference in survival between the two treatment arms (Figure 1). The 1- and 2-year survival was 35% and 13% with MIC/MVP and 39% and 13% with DCb, respectively. The median survival for MIC/MVP was 8.7 months (95% CI 7.7–9.7) and for DCb was 9.5 months (95% CI 7.9–11.1) \( (P = 0.295). \) The median and 1-year survival for patients with performance status 0/1 was 9.1 months (95% CI 7.6–10.6) and 37% for MIC/MVP and 10.8 months (95% CI: 0.3–12.2) and 44% for DCb \( (P = 0.357). \) The median and 1-year survival for performance status 2 patients was 6.6 months (95% CI 6.3–9.7) and 24% for MIC/MVP and 5.0 months (95% CI 3.5–6.5) and 18% for DCb \( (P = 0.952). \)

Response was assessable in 422 eligible patients and was not significantly different between the two arms (Table 2).

**safety analysis**

Complete toxicity data were available for 92.4% of eligible patients and are summarised in Tables 3 and 4. Both regimens were well tolerated with the majority of patients demonstrating only mild to moderate non-haematological toxicity (Table 3). However, the DCb arm was associated with significantly more grade 3–4 alopecia, mucositis and infection. The majority of haematological toxicity (Table 4) was mild to moderate with patients in the DCb arm experiencing significantly more grade 3–4 leucopenia \( (P < 0.005) \) and neutropenia \( (P < 0.005). \) Patients in the DCb arm required significantly more oral and intravenous antibiotics though typically less than one course per patient. Blood and platelet transfusion requirements were similar in each arm. Patients in the DCb arm had significantly more serious adverse events (SAEs) than patients receiving MIC/MVP \( (41\% \text{ versus } 22\%, \ P < 0.005) \) with 105 episodes occurring in 90 patients compared with 53 episodes in 48 patients, respectively. The most frequent SAEs were neutropenia, dyspnoea, haemoptysis, pain, allergic reaction and nausea/emesis. However, there was no statistically significant differences in the rate of reported neutropenic SAEs between the two treatment arms \( (P = 0.138). \) A significantly greater number of overnight stays due to toxicity was noted for patients receiving DCb than MIC/MVP \( (871 \text{ versus } 588, \ P < 0.005). \)

There were 69 early deaths (survival of less than 112 days), the majority being attributable to progressive disease. There were six toxic deaths due to neutropenic sepsis (MIC/MVP 2, DCb 4) and six intercurrent deaths, three in each arm (MIC/MVP—cerebrovascular accident, haematemesis, unknown; DCb—intercerebral haemorrhage, pulmonary embolus, carcinoma trachea).

**QoL**

QoL data is available for 260 patients randomised by the seven centres that agreed to record this prospectively. One hundred and ninety-six (75%) patients completed the baseline forms prior to treatment, 119 patients (61%) completed questionnaires after cycle 1, 81 (41%) after cycle 2, 74 (38%) after cycle 3 and 48 (25%) after cycle 4. The mean overall EORTC score fell in both arms during chemotherapy, but reduced to a less extent in the DCb arm \( (P = 0.021). \) The mean Global Health Status fell in the MIC/MVP arm whereas grade 3–4 alopecia, mucositis and infection. The majority of haematological toxicity (Table 4) was mild to moderate with patients in the DCb arm experiencing significantly more grade 3–4 leucopenia \( (P < 0.005) \) and neutropenia \( (P < 0.005). \) Patients in the DCb arm required significantly more oral and intravenous antibiotics though typically less than one course per patient. Blood and platelet transfusion requirements were similar in each arm. Patients in the DCb arm had significantly more serious adverse events (SAEs) than patients receiving MIC/MVP \( (41\% \text{ versus } 22\%, \ P < 0.005) \) with 105 episodes occurring in 90 patients compared with 53 episodes in 48 patients, respectively. The most frequent SAEs were neutropenia, dyspnoea, haemoptysis, pain, allergic reaction and nausea/emesis. However, there was no statistically significant differences in the rate of reported neutropenic SAEs between the two treatment arms \( (P = 0.138). \) A significantly greater number of overnight stays due to toxicity was noted for patients receiving DCb than MIC/MVP \( (871 \text{ versus } 588, \ P < 0.005). \)

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**Table 1.** Patient and tumour characteristics

<table>
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</tr>
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MIC: mitomycin, ifosfamide, cisplatin; MVP: mitomycin, vinblastine, cisplatin; DCb: docetaxel, carboplatin; ECOG: Eastern Cooperative Oncology Group.

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the DCb arm remained stable with an improvement after cycle 3 (P = 0.014) (Figure 2A–D). Depression increased in both arms over baseline, but the increase was less for the DCb arm (P = 0.021). Anxiety scores reduced in both arms from baseline and was significantly better for DCb (P = 0.005).

Subscales of symptom items that showed a >10% between-treatment difference in the number of patients who improved or deteriorated are displayed as histograms (Figure 3). Comparing baseline to mid-treatment, the DCb arm had a >10% improvement over the MIC/MVP arm in EORTC score, Global Health Status (QL2), role functioning, fatigue, shortness of breath, appetite and constipation. The MIC/MVP arm had more improvement in arm/shoulder pain (Figure 3A). The scores that deteriorated by >10% in the DCb arm were diarrhoea, sore mouth, dysphagia, peripheral neuropathy, hair loss and other pain (Figure 3B). For the MIC/MVP arm, >10% deterioration was in EORTC score, nausea and vomiting, shortness of breath and constipation.

After four cycles of treatment, the >10% between-treatment differences in favour of DCb were Global Health Status, nausea and vomiting, pain, appetite, constipation and LC-13 breathlessness and cough; and with MIC/MVP they were cognitive and social functioning, sleeping, sore mouth and arm/shoulder pain (Figure 3C). A >10% deterioration was seen with DCb for physical and social functioning, diarrhoea, sore mouth, peripheral neuropathy, hair loss, arm/shoulder and other pain; and with MIC/MVP in nausea and vomiting, shortness of breath and cough (Figure 3D).

discussion
This randomised phase III trial compared the newer doublet of carboplatin and docetaxel with what at the time were considered two standard, platinum-based triplet regimens. There was no difference in survival between the two arms, a finding that is in keeping with some [14, 15] but not all [16]...
previous reports of MIC versus other newer agents combined with cisplatin/carboplatin (Table 5). A study comparing cisplatin + etoposide with carboplatin + paclitaxel yielded a similar result, although this may have in part been explained by imbalances in gender and in the use of second-line chemotherapy between the two arms [17, 18]. Despite an increased incidence of infection, mucositis and peripheral neuropathy, patient-reported QoL was better maintained in the DCb than the MIC/MVP treated patients.

The median and 1-year survival in this study is as good as, or better than, that reported in other studies using a similar dose of cisplatin and is not materially different to the two reported studies using cisplatin 100 mg/m² [15, 19]. The study from the London Lung Cancer Group that showed a significant advantage for gemcitabine plus carboplatin over MIC reports the second lowest median survival for MIC (7.6 months) in the five recently reported randomised studies of this regimen (Table 5).

A number of randomised trials have compared a variety of newer platinum based doublets including docetaxel/carboplatin and demonstrated that, in terms of response and survival, no doublet can be considered superior (Table 5) [20–36]. The three-armed TAX 326 study did show a trend towards a survival advantage for cisplatin/docetaxel but not carboplatin/docetaxel over cisplatin/vinorelbine, but was not designed to compare cisplatin/docetaxel with carboplatin/docetaxel [22]. Whether carboplatin can be safely interchanged with cisplatin remains unclear. A recent meta-analysis suggests that cisplatin combined with a newer agent is superior to carboplatin with a newer agent in terms of response rate and survival although no survival advantage was seen in a recent meta-analysis of platinum based versus non-platinum based chemotherapy [37, 38].

Previous studies have shown that MIC/MVP, particularly with cisplatin used at a lower dose, has been a well-tolerated regime with low rates of haematological toxicity and peripheral neuropathy [4, 5]. The incidence of grade 3–4 peripheral neuropathy seen with DCb is consistent with that reported elsewhere for taxane-platinum combinations [19–22]. Grade 3–4 neutropenia was significantly more common with DCb and accompanied by a significant increase in the prescription of oral or intravenous antibiotics. There were four treatment-related deaths due to infection in the DCb arm and two in the MIC/MVP arm. The increased requirement for intravenous antibiotics and nights in hospital may in part be misleading as several centres had neutropenia policies necessitating intravenous antibiotics even in the absence of fever. This is supported by an equivalent rate of neutropenic serious adverse events between the two arms, no significant difference in the
need to dose delay and an equivalent number of cycles administered for each arm. Recent trials in advanced NSCLC confirm high rates of grade 3–4 neutropenia with almost all modern platinum based doublets [20–23, 25]. There was no difference in use of blood products between the two treatment arms.

The interpretation of QoL data is not without difficulties [40–43]. However, when assessed longitudinally it probably represents the best assessment of patient well-being, reflecting the effects over time of previous co-morbidity, disease-related symptoms, performance status and treatment-related toxicity. It may be unrealistic to expect an improvement in QoL with treatment as significant changes in one of the parameters measured, e.g. breathlessness, may not impact on the other dimensions studied. Maintenance of baseline QoL or prevention of treatment-related deterioration in QoL are realistic aims. Comparing QoL between trials can present significant difficulties when different tools and different methods of assessment are used. In this study, we used EORTC QoL, LC13 and HAD. Assessment times were the same for both arms (i.e. 3 weekly), and assessment was carried out mid-cycle, arguably at the time of maximum toxicity. Whilst there was no significance difference between scores across the complete time period examined, both EORTC QoL score and Global Health Status showed a trend towards an advantage for DCb over MIC/MVP after cycle 3, and this was significant for reduction in anxiety, suggesting a benefit for DCb during the treatment period that was lost on follow-up with reversion to the pretreatment values. There was a greater improvement in dyspnoea, fatigue, role functioning, appetite and constipation after cycle 2, and dyspnoea, cough, nausea and vomiting and pain by cycle 4 for the DCb-treated patients. Fatigue was more of a problem for patients treated with MIC/MVP and may have contributed to the significant adverse impact of MIC/MVP upon overall QoL, global health score and physical, role and social functioning. In contrast and despite the significant impact of mucositis, diarrhoea and neuropathy, DCb did not adversely affect these domains, significantly improved emotional functioning by cycle 2 and was supported by data from the HADS scale confirming a greater reduction in anxiety with DCb and increased depression scores with MIC/MVP. Other studies have also shown similar survival but superior QoL for newer doublets over older regimens [17].

Figure 3. EORTC QLC-C30 and LC13 subscales. Items that showed ≥10% between-treatment differences in the proportion of patients reporting (A) improvement and (B) deterioration from baseline to midcycle, and items that showed ≥10% between-treatment differences in the proportion of patients reporting (C) improvement and (D) deterioration from baseline to post cycle 4.
The number of patients studied was small and the dropout rate high, making it difficult to draw reliable conclusions. Missing data are a major problem with QoL, particularly if they are due to a deterioration in the patients condition, these patients are less likely to be compliant with further follow-up data and so follow-up data will be biased [41]. Most analyses assume missing data occur at random. Follow-up QoL data were not available for 40% of patients in this study, in keeping with other published studies [17].

The TAX 326 study presented two measures of QoL: EUROQOL and LCSS [22]. These were measured at different time points for the treatment arms as cisplatin/vinorelbine was administered 4 weekly compared with the 3 weekly docetaxel regimens. Furthermore, the LCSS reports symptoms on the day of assessment, not the previous week, and so may have been influenced by the dexamethasone pre-med given to the docetaxel-based regimen. The absolute differences were modest, typically being less than a 10% difference at individual time points.

This study showed equivalence of the older platinum-based triplet regimen and the combination of docetaxel and carboplatin. Despite greater toxicity in the docetaxel carboplatin arm, QoL was better maintained with this combination.
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references