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Original paper

Northampton outcome for first and second line chemotherapy in non-small cell lung cancer: 5 years data

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Aim of the study: There is a definite improvement of progression-free survival as well as overall survival in treating patients with non-small cell lung cancer (NSCLC) with second line chemotherapy. We reviewed the use of chemotherapy in the first and second line setting at Northampton Oncology Centre with emphasis on the survival benefit. The goal of this retrospective study was to review our clinical practice in delivering multiple lines of therapy in comparison to published data worldwide.

Material and methods: Data were collected from patients' records and the oncology database in Northampton Oncology Centre for patients with non-small cell lung cancer patients. A total of 156 patients' records were studied.

Results: Out of 156 cases, 108 (69.23%) received first line chemotherapy and 48 (30.77%) received second line chemotherapy. Average survival in the first line group was 395 days (13 months) and in the second line group it was 580 days (19 months). There was a difference of 6.1 months (p = 0.04). Also in the first group average time to progression was 8.5 months and in the second group it was 10.5 months, a difference of nearly two months.

Conclusions: Although we have improved the survival of patients who have metastatic NSCLC with our first line treatments, the rate of recurrence and mortality remains high. Second line chemotherapy should be offered in a selected group of patients.

Key words: palliative chemotherapy, non-small cell lung cancer, second line treatment.

Introduction

Lung cancer is one of the most common cancers around the world. In 2008, lung cancer was responsible for 13% (1.6 million) of the total cancer cases and 18% (1.4 million) of cancer deaths. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all cases [1].

The incidence of lung cancer in England and Wales is believed to be 47.4 per 100 000 population [2].

Most cases present with metastatic disease. The 5-year survival rate of this group of patients is 1%, and therefore these patients are generally considered to be incurable. Despite this, the important issues to address include which patients are appropriate for chemotherapy, the survival and palliative impact of chemotherapy, the optimal chemotherapeutic approach, and its toxicity and outcomes expectations [3].

For patients who have a good performance status (PS), chemotherapy has been shown to produce longer survival, palliate disease-related symptoms, and produce a better quality of life than with best supportive care (BSC) [3]. Many patients benefit from initial treatment with chemotherapy, although all patients eventually experience disease progression, generally within a median of 3–6 months of initiating chemotherapy [4, 5].

Nowadays, platinum-based doublet chemotherapy is considered the standard of care for advanced NSCLC. Prognosis after recurrent or progressive disease following first line chemotherapy is usually poor [6].

Adding a second drug improved tumour response and survival rate. Adding a third drug had a weaker effect on tumour response and no effect on survival [7].

Patients who appear more likely to receive second line therapy are those with a good performance status (PS), female patients, and those with non-squamous histology [8].

The goal of this retrospective study was to review our clinical practice in comparison with published data worldwide.

Material and methods

The records of 156 patients with histologically proven non-small cell lung cancer were reviewed. Characteristic of the patients is shown in Table 1. Patients were treated at Northamptonshire Cancer Centre, Kettering General and Milton Keynes General Hospitals. Data were collected from August 2002 to July 2007. Patients were categorized into two main groups: Group one received first line chemotherapy and on recurrence received only palliative radiotherapy or best supportive care (BSC) (108 patients). Group two included patients who received first line chemotherapy and on recurrence received second line chemotherapy plus or minus palliative radiotherapy (48 patients).

Data were obtained from patients' notes and also from the oncology database. Pathology reports were taken from the pathology computerised system. Radiological information was taken from the PACS or IMPAX system. Data collected included: patient's age, sex, smoking habit, date of diagnosis, intention (radical/palliative), type of chemotherapy, date chemotherapy started and date completed, number of first line cycles received, response, date of relapse, date second line chemotherapy started and date it was completed, number of second line cycles, response and lastly date of death and observation. Sites of metastasis were also noted. Patients who had primary surgery were excluded from the study.

Overall survival (OS) from the initial date of histological diagnosis until death was calculated using the Kaplan-Meier method.

Results

In group one, who received first line chemotherapy only, there were 108 patients, 71 male and 37 female patients. Age range was 37–85 years with average of 61 years. There were 47 smokers, 7 non-smokers, 44 ex-smokers, and in 10 patients smoking habit was unknown.

In group two, who received second line treatment, there were 48 patients, 32 males and 16 females. Age range was 38–78 years with average of 58 years. Twenty-three were smokers, 16 ex-smokers, 5 non-smokers, and in 4 patients smoking history was not known.

First line chemotherapy used was platinum based either cisplatin or carboplatin in combination with gemcitabine/vinorelbine. In five patients in group I gemcitabine was used as a single agent. There was no statistically significant difference between the two groups with regard to cisplatin/carboplatin or gemcitabine/vinorelbine ($p = 0.82$).

In the second line setting, docetaxel was the main second line chemotherapy (31 cases). Erlotinib was only used in 5 cases and 12 cases were re-challenged with carboplatin and gemcitabine.

The number of chemotherapy cycles in first line varied from 3 to 6 cycles, while second line cycles varied from 2 to 4 cycles with only one patient receiving 6 cycles. The mean number of chemotherapy cycles for first line in both groups was 4 and the mean number of chemotherapy cycles for patients who received second line chemotherapy was 2.

There was no significant difference between the groups with regard to age, sex, smoking history, stage, histology or number of first line chemotherapy cycles. Stage distribution is shown Table 2 and histology in Table 3.

Table 1. Patient's characteristics

	First line	Second line
Patient numbers	108	48
Average Age/ range	61 (37–85)	58 (38–78)
Sex		
Male	71 (66%)	32 (67%)
Female	37 (34%)	16 (33%)
Performance status		
1	68 (63%)	34 (71%)
2	18 (17%)	3 (6%)
Not reported	22 (20%)	11 (23%)
Smoking habit		
Smoker	57 (53%)	23 (48%)
Ex-smokers	46 (43%)	16 (33%)
Non-smokers	7 (6%)	5 (10%)
Unknown	11 (10%)	4 (8%)
Tumour stage		
IB	1 (1%)	0
IIB	2 (2%)	0
IIIA	14 (13%)	5 (10%)
IIIB	36 (33%)	9 (19%)
IV	58 (54%)	34 (71%)
Histology		
squoumos cell carcinoma	40 (37%)	21 (43.7%)
adenocarcinoma	32 (30%)	18 (37.5%)
large cell carcinoma	6 (5%)	1 (2%)
undifferentiated	30 (28%)	8 (17%)
neuroendocrine	1 (1%)	0

Median survival in the first line group was 395 days (13 months) and in the second line group 580 days (19 months) with a 6-month survival advantage for those treated with second line ($p = 0.04$). The survival curve is shown in Fig. 1.

As expected, patients with longer progression-free survival after first line chemotherapy are more likely to be offered second line chemotherapy and had better overall survival.

In the first line group median time to progression was 255 (8.5 months) days and in the second line group it was 314 days (10.5 months), a difference of 59 days (2 months) ($p = 0.03$).

Discussion

We describe detailed information regarding the clinical course of 156 patients with advanced NSCLC treated with multiple lines of systemic therapy in a 6-year period from August 2002 to July 2008.

Table 2. Showing distribution of the patients according to stages

Stage	First line	Second line	Total	% in first line	% in second line
IB	1	0	1	0.93	
IIB	2	0	2	1.85	
IIIA	14	5	19	12.90	10.42
IIIB	36	9	45	33.33	18.75
IV	58	34	91	53.70	70.83
total	108	48	156	69.23	30.77

Table 3. Showing histological distribution in the two groups

Histology	Group I	Group II
squmous cell carcinoma	40 (30.04%)	21 (43.75%)
adenocarcinoma	32 (29.63%)	18 (37.5%)
large cell carcinoma	6 (5.56%)	1 (2.08%)
undifferentiated	30 (27.78%)	8 (16.67%)
neuroendocrine	1 (0.93%)	0

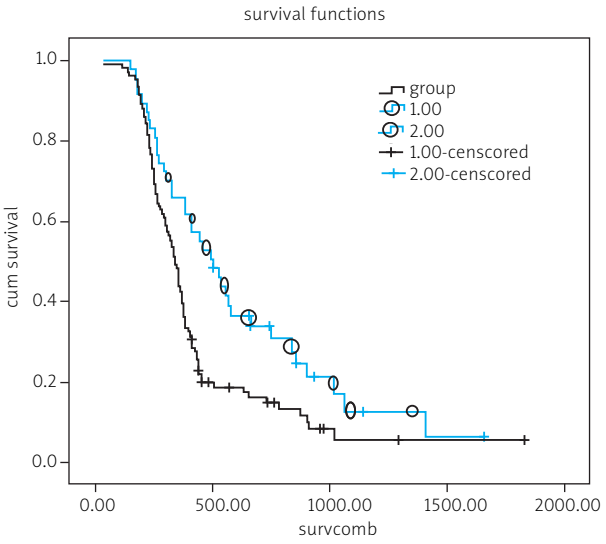

Fig. 1. Kaplan-Meier survival

The male to female ratio in our study is 2 : 1 while in the UK the male : female ratio was > 6 : 1 in 1973 compared with 1.5 : 1 in 2008 [9].

With regard to histology, squamous cell carcinoma represents 39% in our series while adenocarcinoma represents 26%, large cell 4%, and undifferentiated NSCLC 24%. The published national figures are [9]: squamous cell carcinoma represents 32%, adenocarcinoma 26%, non-specified NSCL 35%, large cell carcinoma 4% and bronchoalveolar carcinoma 2%.

In our series the median survival for patients who received first line only was 395 days (13 months) and in the second line group 580 days (19 months) with a 6-month survival advantage for those treated with second line.

In a similar UK retrospective trial by Eccles *et al.* [10], the median survival for the 110 patients receiving palliative chemotherapy as their first oncological treatment was 10 months (95% confidence interval [CI]: 8.6–11.4 months). Of note, for patients who received more than one line of therapy, median OS was 16 months (95% CI: 14–17.9).

The median survival for individuals with lung cancer in England is 203 days. Contemporary data reveal that 32% of male patients and 35% of female patients survive to one year in England [9].

Despite demonstrated improvements in first line treatment, most stage IIIB/IV patients experience disease progression and 50–60% of them are fit enough to receive a second line treatment [11]. In our study 30% of patients had second line chemotherapy. Hensing *et al.* [8] studied 230 patients with stage IIIB or IV NSCLC who received first line therapy with carboplatin and paclitaxel. Of these patients, only 101 (44%) received second line therapy.

The impact of second line chemotherapy has been studied in a large cohort of 4,318 patients in 19 phase III trials [11]. A median survival time of 6.6 months showed no correlation with the objective response rate (p50.6992) but, in contrast, was better associated with the disease control rate (p50.0129). This indicates that not only tumour shrinkage, but also disease stabilization, contributes to survival benefit in the second line setting.

This 6.6-month advantage of second line correlates with our 6-month survival advantage and also data published by Eccles *et al.* [10].

While the prognostic factors associated with improved survival with first line therapy have been extensively studied, less information exists about the prognostic factors in second line therapy. For the treating physician, prognostic factors may assist in determining the likelihood of clinical benefit of further therapy [12].

In our series, patients with longer progression-free survival after first line chemotherapy are more likely to be offered second line chemotherapy and had better overall survival. This is in agreement with data of Hensing *et al.* [11], who defined factors increasing the likelihood of second line therapy including high performance status, female sex and non-squamous histology, while early termination of first line therapy decreased the likelihood of further therapy. In another study [13], sex, stage at diagnosis, performance status at the start of second line therapy and best response to initial therapy were associated with improved survival outcome in multivariate analyses. Thus, these factors should be used to select the patients who will benefit most from second line chemotherapy.

Docetaxel was the main second line used in our series. The reason is that docetaxel was the only NICE-approved second line during the study period. It was also considered the gold standard worldwide second line agent [14–17].

Pemetrexed was known to be a very popular second line treatment prior to its endorsement as first line in adenocarcinoma in recent years. It is well tolerated even in elderly with manageable side effects [18].

Erlotinib is currently the main competitor in second line chemotherapy, with more tolerability. There have been some reports suggesting that the application of radiotherapy in first line treatment has predictive rather than prognostic value for the efficacy of erlotinib in second or third line therapy [19].

Although we have improved the survival of patients who have metastatic NSCLC with our first line treatments, the rate of recurrence and mortality remains high. Second line chemotherapy should be offered in a selected group of patients. Further studies are needed to further improve the overall survival of this group of patients.

The authors declare no conflict of interest.

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