Altounyan address

Clinical trials in lung cancer: nihilism versus enthusiasm

Stephen G Spiro

In the mid 1950s Roger Altounyan began work on a natural compound, khellin, the active constituent of an Eastern Mediterranean plant, *Ammi visnaga*, which had been known since Biblical times to have bronchodilator properties. However, its side effects outweighed any potential beneficial effects and the project was abandoned until 1964 when it was reinstated under Fison's management. By 1965 Altounyan had identified sodium cromoglycate as a potential substance protective against asthma (but not a bronchodilator) with sufficiently long duration of action to be clinically useful. Roger, being asthmatic, tested this and most other possible compounds on himself. Clinical trials with cromoglycate began soon afterwards.

My own interest in clinical trials provided the stimulus for the establishment of the London Lung Cancer Group in 1979. Over the next 18 years we carried out several large studies looking at the effects of chemotherapy on survival, morbidity, and quality of life in patients with small cell lung cancer (SCLC) and, over the last 10 years, have begun to investigate the effects of chemotherapy in non-small cell lung cancer (NSCLC).

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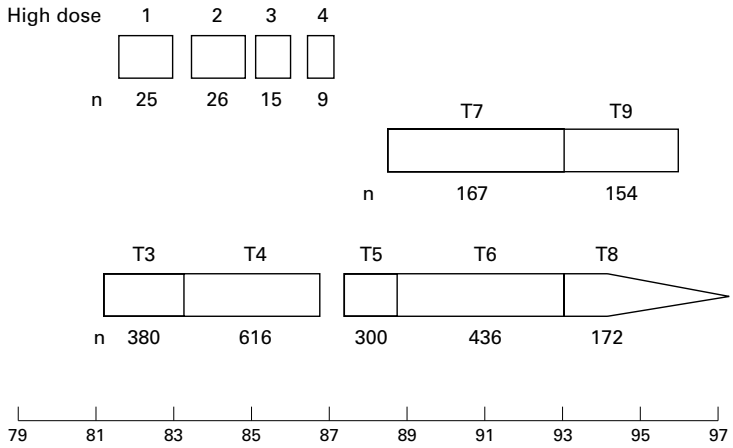

Figure 1 London Lung Cancer Group trials in small cell lung cancer since 1979. T3 = chemotherapy versus chemotherapy and radiotherapy; T4 = short versus long course chemotherapy; T5 = six courses of chemotherapy versus chemotherapy 'as necessary'; T6 = six courses of three weekly chemotherapy versus 12 courses of weekly chemotherapy in good prognosis patients; T7 = six courses of three weekly chemotherapy versus 12 courses of 10–11 day chemotherapy in patients with extensive disease; T8 = six courses of chemotherapy with early versus late radiotherapy; and T9 = six courses of chemotherapy versus six courses of oral etoposide.

Small cell lung cancer

I will first summarise some important points learnt from the work of our group and of others in SCLC and will then proceed to discuss the difficulties we have in transforming this approach to the much more common constellation of lung cancers that comprise NSCLC.

Figure 1 summarises the studies that the London Lung Cancer Group have carried out in small cell lung cancers. I shall comment briefly on the value of the addition of radiotherapy to chemotherapy in SCLC, the optimum duration of chemotherapy, and the intensification of chemotherapy, including our studies on high dose chemotherapy and also the recent studies of less intensive chemotherapy with oral etoposide in patients with a poorer prognosis.

THE ROLE OF RADIOTHERAPY IN ADDITION TO CHEMOTHERAPY

Between 1981 and 1983 366 patients with either limited disease or extensive disease SCLC were entered into a randomised study of either 12 courses of chemotherapy alone or the same chemotherapy but with 40 Gy radiotherapy given between courses four and five.[1] The results of this study were published in 1984 and showed no survival advantage for the addition of radiotherapy to chemotherapy (fig 2). However, when re-analysed eight years later as part of a meta-analysis with 12 other studies of similar design[2] there was a significant advantage in favour of the addition of radiotherapy ($p<0.001$). The survival advantage for patients who had also received radiotherapy was 5.4% at three years and was greatest in younger patients, but tended to be lost in those over 70 years of age at diagnosis. This analysis showed that, in order to identify a small but important survival advantage, large numbers of patients were needed to be analysed, particularly in a disease with the early lethality of SCLC. The meta-analysis included approximately 2100 patients. This survival advantage of 5% has been a major influence in establishing radiotherapy as a routine procedure in responding patients with SCLC and appears to be perfectly appropriate. There is still some discussion as to the optimal dose of radiotherapy and of the timing during chemotherapy.[3] The latter question is being further

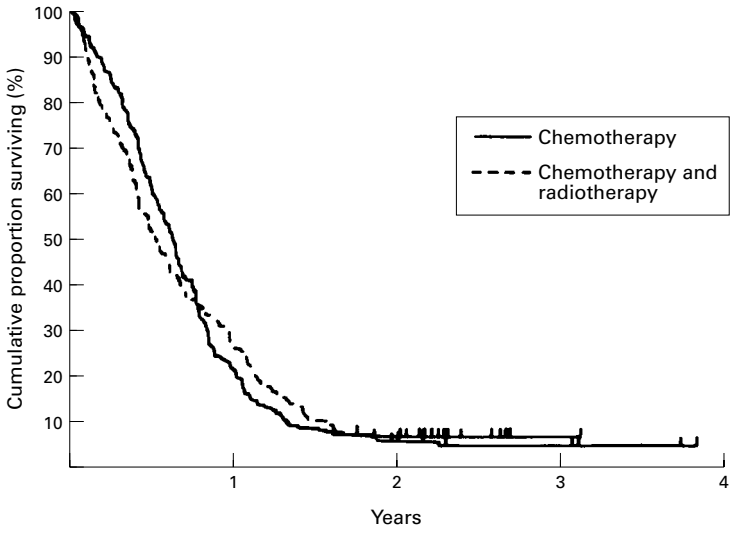

Figure 2 Survival in all patients allocated to receive chemotherapy alone or both chemotherapy and radiotherapy. Reproduced from Souhami et al[1] with permission.

assessed in our current London Lung Cancer Group study.

Another useful management tool that emerged from this study was the identification of prognostic factors based on simple parameters including routine blood test analysis and performance status at diagnosis that allowed the separation of patients into good, intermediate, and poor prognostic categories (table 1). These prognostic factors were just as discriminating as the more complex staging procedures then in use, including bone marrow aspiration/trephine, bone scans, and computed tomographic (CT) scans of thorax, brain and abdomen. They allowed clear separation between those patients with a good and a poor prognosis (fig 3A and B),[4] those with a good prognosis having a four year survival of 18% compared with virtually no survivors beyond 18 months amongst patients in the poor prognosis category. The challenge remains to improve the survival of patients with a good prognosis. Much time and energy has already been spent on studies of intensification of chemotherapy, alternating non-cross resistant chemotherapy regimens and the intensification of chemotherapy with colony growth stimulating factors to try to squeeze a better four to five year survival from this group of patients.

OPTIMAL DURATION OF TREATMENT WITH CHEMOTHERAPY

In 1983 it was still common to treat patients with chemotherapy for one year after the establishment of a complete response, whilst those in only a partial remission would often continue treatment until relapse. Prolonged courses of chemotherapy were debilitating and even 12 courses, as in the study described above, were onerous. Several groups then attempted to minimise the duration of chemotherapy without compromising response rates or median survival. Our group evaluated randomisation to four or eight courses with a further randomisation to either additional but different chemotherapy on relapse or best supportive care.[5] The MRC Lung Cancer Working Party compared six and 12 courses of chemotherapy.[6] The Midlands Lung Cancer Group gave six courses with randomisation to just follow up or to an additional eight courses[7] and later, in 1993, the MRC compared three courses with six courses of chemotherapy.[8] The upshot of all these and other studies was that six courses seemed optimal, with a complete response being achieved in 50% of patients who presented with limited disease and an overall response rate of 80–90% with no reduction in median survival. Chemotherapy comprising less than six courses appeared to be inadequate, particularly for the responding populations whose disease free interval was less than after six or more courses. This was a valuable step forward as it was associated with less cumulative toxicity for the patient, shorter time in hospital and, therefore, cheaper care.

Table 1 Prognostic indicators in small cell lung cancer

	Good	*Intermediate*	*Poor*
Performance status	High	High	Low
Serum levels:			
Sodium			
Albumin	Normal	One variable abnormal	
Alkaline phosphatase			

INTENSIFICATION OF CHEMOTHERAPY

Treatment "when necessary"

Our group then carried out several studies on the effects of varying the intensity of chemotherapy. In 1987 there was concern over the toxicity of chemotherapy and the fact that most patients with SCLC who received chemotherapy were still doomed to die of their disease. We considered whether the intensity of chemotherapy could be reduced with no adverse effect on survival but with better tolerance of chemotherapy, fewer side effects, and an improved quality of life. One study design incorporated our now standard regimen of six courses of chemotherapy, each course given every three weeks, versus an experimental arm comprising an initial course of chemotherapy followed by treatment only "when deemed necessary".[9] Chemotherapy would be given if tumour specific symptoms were not controlled by the first course of chemotherapy, if symptoms that had been controlled recurred, or if the physician felt that there was sufficient radiological, biochemical or other change due to disease that suggested a further course of chemotherapy was indicated. The study showed that the intensity of treatment in the "as necessary" arm was exactly half of the regular three weekly arm. The two survival curves were similar, but the main difference was in quality of life. This study was one of the first to use a simple diary card system for the assessment of quality of life. The card comprised eight questions with the answers on a scale of 1–4, a higher value indicating poorer quality of life.[9] The diary card was adapted from an earlier version produced by the Medical Research Council.[9,10] The suc-

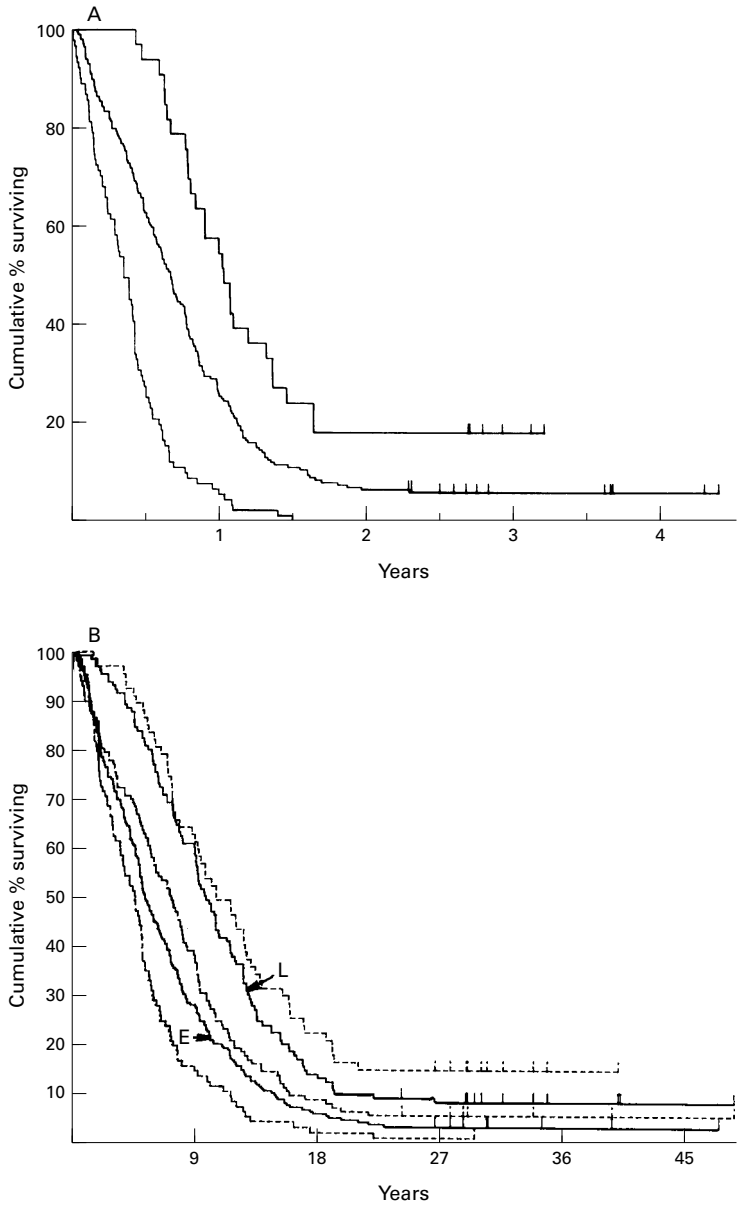

Figure 3 Survival related to (A) good, intermediate and poor prognostic categories and (B) the three prognostic categories defined in (A) in relation to the extent of the disease (L = limited; E = extensive). Reproduced from Souhami et al[4] with permission.

cess of the adapted diary card was particularly good as we concentrated on measuring quality of life in just one centre and the patients were followed individually by a clinical nurse specialist. The quality of life data were worse in the "as necessary" arm for pain, mood, well being, anxiety, depression, and sleep quality, but not for activity.[9] This result indicated that regular chemotherapy was better for controlling symptoms than chemotherapy given only when the physician felt that it was appropriate (fig 4).

Weekly chemotherapy

The London Lung Cancer Group's next study was a reversal of this philosophy. Six courses of three weekly chemotherapy were again taken as standard and patients were randomised to this arm or an alternative of weekly chemotherapy for 12 weeks.[11] The cumulative dosage in the two arms was different as the weekly chemotherapy was intended to be considerably more than in the three weekly schedule. This attempt to improve response and survival by intensifying treatment was confined to patients with a good prognosis.

Analysis of the results showed that the dose intensity for the three weekly arm was 96% of intended but, for the weekly arm, was only 73%. Only a small fraction of patients received the intended dose of weekly chemotherapy exactly as planned. Most of the patients either had treatment delays or dose reductions (according to white cell and platelet parameters). There was a useful message here that dose intensification studies need to be analysed on the intention to treat, but have to be interpreted on the actual doses of chemotherapy received by the patients. In our study the survival between the weekly and three weekly chemotherapy regimens was identical but, once again, the diary card quality of life assessment showed considerably poorer quality of life for the patients receiving weekly treatment in all variables measured. Subsequent attempts to intensify chemotherapy successfully have included supporting the patients with colony growth stimulating factors (G-CSF, GM-CSF) to shorten periods of neutropenia and to minimise the risk of infection. However, whilst this has been successful, it has not been reflected in better survival data.

High dose intensification chemotherapy

Since 1979 we had been particularly interested in high dose intensification treatment for patients with good prognosis limited disease SCLC. Four high dose studies were carried out over a six year period. Patients were protected by autologous bone marrow transplantation with marrow harvested before chemotherapy after a negative marrow aspirate. Marrow was re-infused the day after high dose chemotherapy. Our initial study comprised the administration of 200 mg/kg cyclophosphamide and, on recovery, 40 Gy radiotherapy to the primary tumour site. Thoracic CT scans carried out before and three weeks after chemotherapy showed an 80% reduction in tumour volume. The second study was of similar design but with two identical consecutive courses of high dose cyclophosphamide.[12] Again, this was well tolerated and CT scanning showed a similar reduction in tumour volume following the first dose of cyclophosphamide, but no further effect was seen after the second course. Median survival was also not improved. It seemed, therefore, that tumour resistance was the main reason for failure to improve median survival, although a considerable reduction in tumour burden was achieved by the first high dose chemotherapy while the second treatment had no discernible effect.

The third and fourth studies involved induction chemotherapy followed by high dose chemotherapy (cyclophosphamide or melphalan). Neither of these studies, admittedly

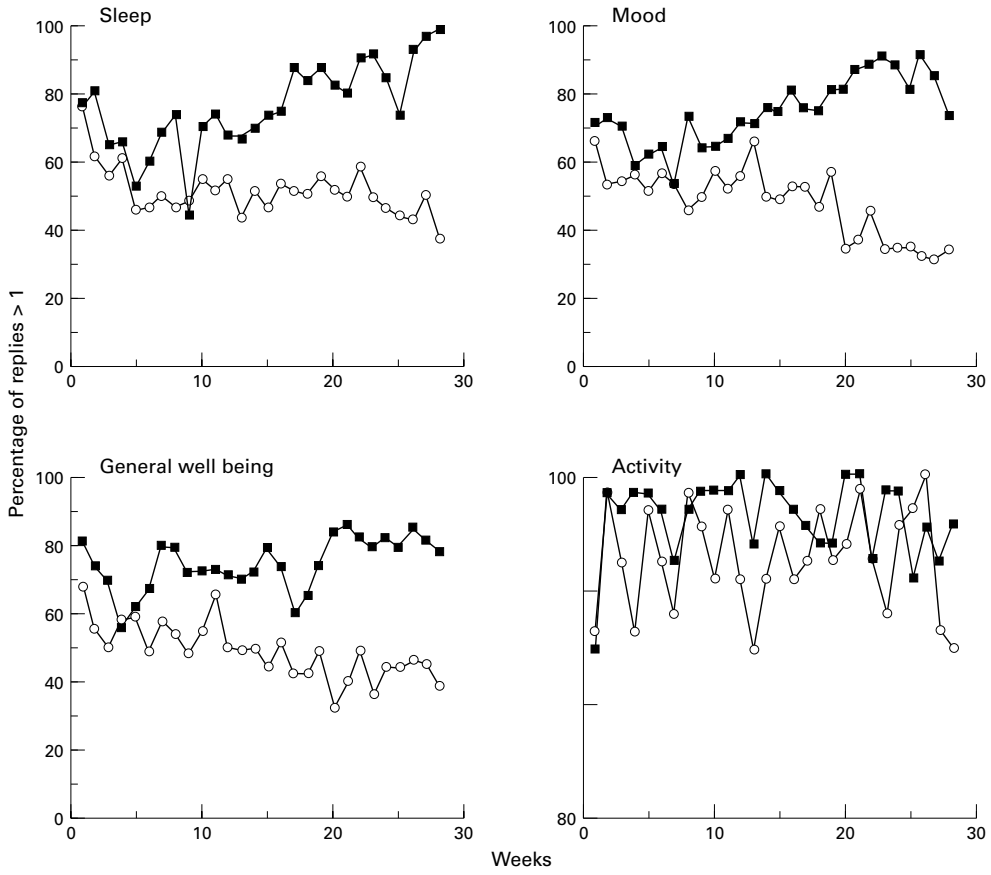

Figure 4 Percentage of weekly scores reporting symptom grades 1 or more for sleep, mood, general well being, and activity. Mood, sleep, and general well being were adversely affected in the 'as required' group (■) and activity was worse in the planned chemotherapy group (○); note that activity is scored in the opposite direction to other symptoms, a high score indicating more activity. Reproduced from Earl et al[9] with permission.

uncontrolled and in patients with a good prognosis, showed any better median survival than the response, in general, to routine standard three weekly chemotherapy for all patients with limited disease who had entered our large studies that were running simultaneously (fig 5).

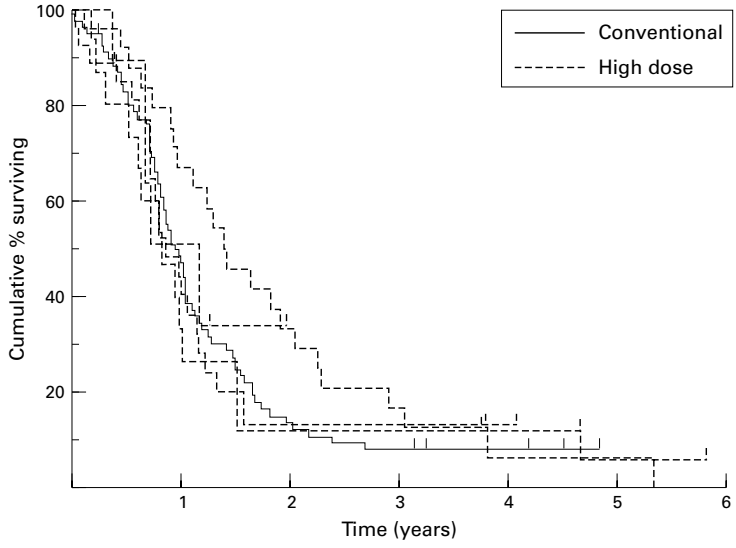

Figure 5 Survival curves of four high dose chemotherapy trials and the overall survival of patients with limited disease treated in studies 3 and 4 showing no overall differences.

This series of studies leaves considerable doubt as to whether high dose chemotherapy will ultimately be more effective than conventional chemotherapy.

Oral etoposide

Our most recent study was based on the high activity and response rate of the oral agent, etoposide. This drug, although unpredictable in its absorption profile and its toxicity, is increasingly used for treating patients who are elderly or have a poor prognosis, or both. The London Lung Cancer Group and the MRC Lung Cancer Working Party conducted studies to compare conventional intravenous chemotherapy – that is, six courses given three weekly – with different regimens of oral etoposide.[13 14] Both studies have been stopped prematurely by a Data Monitoring Committee because of poorer median survival or poorer quality of life parameters, both in the oral etoposide groups. The administration of this agent as single oral therapy is no longer recommended in the management of SCLC – at least as an isolated treatment.

CONCLUSIONS

In summary, we have been involved in several developments in the management of SCLC.

High dose chemotherapy appears to be little better than conventional chemotherapy. Mediastinal radiotherapy improves median and long term survival, but the question of optimal timing of the radiotherapy is still being addressed. Simple prognostic factors at diagnosis can identify patients who are likely to do well and these factors should influence the type of clinical trial or chemotherapy regimen they receive. For patients outside clinical trials, six courses of chemotherapy are adequate and optimal. Lesser or greater intensity of chemotherapy appears to have little effect on median survival but an adverse effect on the quality of life. Further reducing the intensity by using the oral single agent etoposide in patients with a moderate or poor prognosis also appears to be inferior to conventional intravenous chemotherapy.

Non-small cell lung cancer

The role of chemotherapy in NSCLC is uncertain, particularly amongst respiratory physicians in the UK. There are many centres throughout the world who have no doubt whatsoever that patients with NSCLC should, whenever possible, be given chemotherapy almost independent of the stage at which the disease presents. However, because of the scepticism for the value of chemotherapy in Britain today, it is still possible to evaluate the role of chemotherapy in NSCLC in a controlled manner.

There are, however, several other factors which influence the management of NSCLC – namely, age, who makes the diagnosis, physician prejudice, organisational ability/desire, informed consent/ethics, and the fact that treating NSCLC is time consuming.

AGE

A recent study by Brown *et al*[15] showed that, in the Southend district, the mean age of patients at presentation with lung cancer is gradually increasing. In general, by the year 2000 more than 40% of new diagnoses worldwide will be made in patients over the age of 75 years. The incidence of lung cancer in women is also increasing. Nevertheless, Brown *et al*[15] showed that age remains a major disincentive for advising active treatment. When allowing for similar performance status they observed that, whilst 65% of patients under the age of 65 and 46% over the age of 75 had an ECOG status of 0, the percentage of these patients treated was 86% and 39%, respectively. There are very few data on the response rate, toxicity, and median survival for elderly patients receiving treatment for either SCLC or NSCLC. What few data there are suggest that, stage for stage and allowing for performance status, there is no disadvantage to elderly patients in receiving chemotherapy, yet most clinical trials state an upper age limit of 70 or 75 years.[16 17]

WHO MAKES THE DIAGNOSIS?

An editorial[18] reported that, in the Leeds area of Yorkshire, the chances of a diagnosis of lung cancer being made was 50% greater if patients were sent to a thoracic physician than one of 85 other consultants who each saw less than 10 new cases of lung cancer per year (none were thoracic physicians). Furthermore, this non-specialist group referred fewer than half the number of patients to surgery than did the thoracic physicians, and sent 20% compared with 38% for radiotherapy, and 6% compared with 10% for chemotherapy. Thus, referral to a non-specialist substantially reduces the patient's chances of getting appropriate treatment. Another similar type of study that looked at the number of patients treated by surgery or other means in the North East Thames region showed a difference of up to 100% across the districts in the region as to whether patients received surgery or radiotherapy or chemotherapy (Rudd, personal communication). This gross variation in patients being referred for treatment was not due to any specific deficiency such as lack of thoracic physicians, radiotherapists or oncologists, but appeared to be due merely to local practice.

PHYSICIAN PREJUDICE

In December 1995 a large meta-analysis was published of 52 randomised studies which included surgery, radiotherapy, or best supportive care in which there was a randomisation to receive or not to receive additional chemotherapy.[19] The results of this study suggested that modern chemotherapy (defined as combination chemotherapy containing cisplatin) provided a significant survival advantage for the addition of chemotherapy to surgery, chemotherapy to radical radiotherapy, and also improved the median survival for patients with advanced disease who received chemotherapy compared with those given only best supportive care.

Following the publication of these findings, Crook *et al* (Girling, personal communication) sent a questionnaire posing three clinical scenarios in NSCLC to ascertain the treatment habits within the UK. Of 821 clinicians surveyed, 454 of those who replied were directly involved in the treatment of lung cancer including 220 respiratory physicians, 153 radiotherapists, 59 cardiothoracic surgeons, 26 medical oncologists, and seven palliative care physicians. The questions and responses are summarised in table 2.

For case 1 less than 1% of responders were prepared to consider adjuvant chemotherapy to surgery with 74% wishing to offer no further treatment. All respondents had no expectation that adjuvant treatment would influence survival. The meta-analysis, however, suggested that a highly significant 5% survival advantage at five years could be obtained by the addition of chemotherapy to surgery compared with surgery alone.[19] If substantiated, this would represent one of the largest improvements by a single modality change in the treatment of NSCLC in recent years. Yet, just some months after publication, it had no discernible effect on treatment habits.

In case 2, a locally advanced inoperable squamous cell cancer, most doctors chose

Table 2 Summary of questions and treatment responses in three hypothetical cases of lung cancer

	Case 1	*Case 2*	*Case 3*
	Male, 65 years, squamous cell, T2N1M0, resected by pneumonectomy; hilar node involved	Male, 65 years, squamous cell, T2N3M0	Male, 65 years, squamous cell, ECOG 0, minor haemoptysis, bone scan positive in humerus (biopsy positive) and skull
Would you recommend			
No further treatment	74%		
Chemotherapy	<1%	11%	
Radiotherapy	24%	68%	11% (26% if aged <50)
Radiotherapy and chemotherapy	0	9%	
	No expectation of adjuvant treatment influencing survival		

radiotherapy as their initial treatment and only 11% chose chemotherapy. Only 9% were prepared to consider the combination of chemotherapy and radiotherapy. Once again the meta-analysis had shown a small but significant sustained survival advantage for the combined approach of chemotherapy and radiotherapy.[19] Additional studies are still in progress to increase the numbers of patients submitted to the randomised addition of chemotherapy to radiotherapy. However, most respondents to the questionnaire of Crook *et al* were not prepared to consider adding chemotherapy to radiotherapy.

The treatment choice for case 3, an otherwise fit patient with a single biopsy proven metastasis and a possible further lesion shown on a bone scan in the skull, was even more striking. Only 11% chose chemotherapy as an option following diagnosis and staging, with 26% electing to give it if the patient was under 50 years of age. There is no evidence that younger patients have a better response and survival than older ones! Here again, the meta-analysis showed an improvement in survival (10% at one year) with the addition of chemotherapy to best supportive care, and this survival advantage was still maintained (although smaller) at two years.

The responders to the three questions were also asked how large an improvement in survival would be required for each clinician to begin to use chemotherapy routinely (table 3). The majority demanded an improvement in survival after chemotherapy of more than 10% before adopting this modality (62% for case 1, 37% for case 2, and 64% for case 3). These expectations are quite unrealistic and far greater than anything yet achieved for any other solid tumour. It seems that our expectations for chemotherapy are exaggerated and the huge impact of improved median survival of just a few percentage points in such a common disease is lost on most physicians who treat lung cancer.

Table 3 Improvement in survival rate of NSCLC with chemotherapy required for clinicians to adopt such treatment routinely (%)

Additional benefit (%)	*Case 1*	*Case 2*	*Case 3*
0–5	12	25	9
6–10	25	37	28
11–15	20	27	21
16–20	23	6	23
21–25	8	3	5
26–100	11	1	15
	62%	37%	64%

It is precisely with this indifference and uncertainty in mind that the Big Lung Trial has been organised throughout the UK and in some European centres. The study proposes to pose prospectively the same question as the meta-analysis attempted to answer from retrospective data. It is hoped to recruit 10 000 patients from all those involved in the care of NSCLC in whom there is doubt concerning the efficacy of chemotherapy.

However, much needs to be achieved before large numbers of patients with NSCLC can be treated in an organised manner in national or international studies. First, all potential new cases of lung cancer need to be referred to respiratory physicians for diagnosis and assessment. These physicians need to organise a specific multidisciplinary lung cancer clinic for the supervision of patient care. In particular, they should provide the patient with the diagnosis and therapeutic options within the shortening period of time that most health authorities now recommend following the Calman report.[20]

There are pressures and difficulties over obtaining full and informed consent before entering anxious, often uncertain, and even depressed patients into a clinical trial, especially when one option is less treatment – that is, no chemotherapy – compared with more treatment – that is, to receive chemotherapy. Several visits may be necessary to explain and achieve this, all of which is time consuming and needs to include collaboration with a nurse specialist or palliative care nurse as well as the involvement of the patient's partner and close relatives.

Of the initial recruits to the Big Lung Trial, only a few have entered the surgical/adjuvant chemotherapy arm of the study. This may stem from poor communication between the referring physician and the cardiothoracic surgeon, or may be because patients have not come back within the stipulated six weeks following surgery – a criterion for entry into the study. It appears, however, that much closer collaboration with the cardiothoracic surgeons is essential to ensure that all parties, including the patient, are made aware of the treatment plan – especially if subsequent entry into a clinical trial is envisaged following resection.

Conclusions

We still have a considerable way to go until we have achieved optimal management for the patient with lung cancer, and major questions

regarding basic treatments remain, some of which appear not even to be open to serious consideration by most respiratory physicians. There remains, however, a real need for the continuation of large randomised clinical trials.

L James, N Gower, M-C Ruiz de Elvira, M McCarthy, K Ask, K Law, H Quinn, C Pickering, W Burford, and S Barton have given invaluable support as nurse clinical coordinators or data managers over the last 20 years.

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