THE LUNG CANCER PARADOX: TIME FOR ACTION

R C Rintoul, T Sethi

Introductory articles

Management and survival of patients with lung cancer in Scotland diagnosed in 1995: results of a national population based study

A Gregor, CS Thomson, DH Brewster, PL Stroner, J Davidson, RJ Fergusson, R Milroy on behalf of the Scottish Cancer Trials Lung Group and the Scottish Cancer Therapy Network

Background: The prognosis of patients with lung cancer in Scotland is poor and not improving. This study was designed to document factors influencing referral, diagnostic evaluation, treatment, and survival in patients with lung cancer. Methods: Patients diagnosed during 1995 were identified from the Scottish Cancer Registry and their medical records were reviewed. Adequate records were available in 91.2% of all potentially eligible cases. Results: In 1995, patients in Scotland with lung cancer had a high rate of microscopic verification (74.1%) and 75.3% were assessed by a respiratory physician; however, only 56.8% received active treatment (resection 10.7%, radiotherapy 35.8%, chemotherapy 16.1%) and 2.9% participated in a clinical trial. Survival was poor with a median of 3.6 months; 21.1% (95% CI 19.8% to 22.4%) were alive at 1 year and 7.0% (95% CI 6.2% to 7.8%) at 3 years. Management by respiratory physician, oncologist, or thoracic surgeon was an independent predictor of access to potentially curative treatment and better survival. Conclusion: This national population based study demonstrates low use of treatment, poor survival, and the influence of process of care on survival. Implementation of evidence-based guidelines will require substantial changes in practice. Increasing the number of patients who receive treatment may improve survival. (Thorax 2001;56:212–7)

Platinum-based and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicentre trial

V Georgoulias, E Papadakis, A Alexopoulos, X Tsiafaki, A Rapti, M Veslemes, P Palamidas, I Vlachonikolis; Greek Oncology Cooperative Group (GOCG) for Lung Cancer

Background: Docetaxel in combination with cisplatin or gemcitabine are active chemotherapy regimes against non-small-cell lung cancer. We compared the efficacy and safety of a combination of cisplatin and docetaxel (group 1) with that of gemcitabine and docetaxel (group 2) in the treatment of advanced non-small-cell lung cancer in a prospective, randomised, multicentre trial. Methods: Patients with stage IIIB or IV lung cancer who had not had prior chemotherapy were allocated either to group 1 and treated with docetaxel (100 mg/m², day 1) and cisplatin (80 mg/m², day 2) or to group 2 and treated with gemcitabine (1100 mg/m², days 1 and 8) and docetaxel (100 mg/m², day 8). All patients received recombinant human granulocyte colony-stimulating factor (150 µg/m²) and had appropriate standard premedication. Response and toxicity were assessed using WHO criteria. Analysis was by intention to treat. Findings: 441 patients were randomly assigned to receive docetaxel/cisplatin (group 1, n=219) or gemcitabine/docetaxel (group 2, n=222). 14 patients in group 1 and 21 patients in group 2 were not evaluable. Objective response rates were similar in the two groups: group 1, 32.4% (95% CI 26.2–38.6%); 1.4% complete response and 31% partial response); group 2, 30.2% (24.5–36.2%; 0.9% complete response and 29.3% partial response). The two groups did not differ in median duration of response, time to tumour progression, overall survival, or 1 year or 2 year survival rates. Interpretation: Both drug combinations had comparable activity in patients with advanced cancer who had not previously had chemotherapy; however, gemcitabine and docetaxel had the most favourable toxicity profile. (Lancet 2001;357:1478–84)
BACKGROUND

Lung cancer is now the most common fatal malignant disease in the developed world, causing upwards of 40,000 deaths in the UK per annum. In the West the incidence of lung cancer in men is beginning to fall, but the incidence in women continues to rise. In developing nations where smoking rates are high, mortality from lung cancer has been rising steadily and this rise is expected to continue well into this century. Approximately 25% of cases are small cell lung cancer (SCLC), while the remaining 75% are classified under the umbrella term of non-small cell lung cancer (NSCLC).

SCLC is considered to be a systemic disease with about 70% of patients having metastases at the time of presentation. The cornerstone of treatment is chemotherapy. In 1969 the Veterans’ Administration lung cancer study group reported that the single agent cyclophosphamide produced a doubling of mean survival time compared with a placebo controlled group. Since then some 15–20 cytotoxic agents have been shown to have major activity against SCLC. Although a number of regimens produce similar responses, combinations containing etoposide are well tolerated and highly active. The combination of cisplatin and etoposide is the most accepted regimen in the UK today. For patients with limited stage disease who have achieved a complete response to chemotherapy, it is usual to give a course of radiotherapy to the mediastinum and the site of primary disease. A meta-analysis of 2103 patients in 13 trials revealed a survival advantage of 5.4% at 3 years for those who had received radiotherapy in addition to chemotherapy. Consolidation radiotherapy is now a routine procedure in responding patients with limited stage SCLC. However, despite aggressive combined modality chemotherapy, the median ranges of survival for limited and extensive disease are 14–20 months and 8–13 months, respectively.

In marked contrast to SCLC, long term survival in patients with NSCLC can be up to 70% depending upon stage. Following surgical resection alone, 5 year survival rates of up to 67% for stage I disease and up to 55% for stage II disease are reported. For patients unable to undergo surgery, radical radiotherapy with intent to cure has been the most common approach with 2 year survival of 54–93% and 5 year survival of 13–39%.

Although survival rates in patients with early stage disease are encouraging, the majority of patients present with locally advanced or metastatic disease which precludes surgery. While stage IIIB disease is unresectable, stage IIIA disease may be resectable and, whenever possible, should be treated with curative intent. Previously, stage IIIB disease was treated with the aim of cure by radiotherapy alone. However, due to the presence of unrecognised micrometastatic disease at presentation, relapse at the primary or distant sites was commonplace, resulting in median survival times of 10 months or less and 5 year survival rates of 5–10%. Survival beyond 5 years occurs in only 3–8% of patients.

In marked contrast to SCLC, long term survival in patients with NSCLC can be up to 70% depending upon stage. Following surgical resection alone, 5 year survival rates of up to 67% for stage I disease and up to 55% for stage II disease are reported. For patients unable to undergo surgery, radical radiotherapy with intent to cure has been the most common approach with 2 year survival of 54–93% and 5 year survival of 13–39%.

In 1995 a meta-analysis using updated individual patient data on 9387 randomised cases from 52 available trials was therefore conducted by the Non-Small Cell Lung Cancer Collaborative Group in an attempt to evaluate the effect of cytotoxic therapy on survival. This study suggested that combination chemotherapy containing cisplatin provided a significant survival advantage in combination with either surgery or radical radiotherapy in stage I and II disease. Furthermore, platinum based chemotherapy improved the median survival for patients with advanced disease who received chemotherapy compared with those given supportive care. The absolute survival benefit for radical radiotherapy and chemotherapy was 4% at 2 years. The absolute benefit for supportive care and chemotherapy was 10% at 1 year, suggesting that cisplatin based regimens can improve survival and should form part of standard treatment.

Despite these findings, there has been little change in the 5 year survival for lung cancer since George VI died from it in 1952. In the UK fewer than 5% of patients are alive 5 years after diagnosis. This figure compares poorly with the 5 year survival rates of up to 14% reported by some European countries.

Management and survival of lung cancer patients in Scotland in 1995

The study by Gregor and colleagues (first Introductory article) examines factors influencing referral, diagnostic evaluation, treatment, and survival of patients diagnosed with lung cancer in Scotland during 1995. This is the first national study of its kind and documents a baseline of clinical practice before the development and dissemination of evidence-based clinical guidelines.
for the management of lung cancer. The information used was collected from standard hospital and primary care records and, as with any retrospective data collection system, was limited in some aspects such as case note availability/adequacy and the availability of certain prognostic factors such as performance status, accurate staging, and co-morbidity. However, despite these problems, over 91% (3855/4465) of eligible cases were evaluated. Of patients evaluated, 2188 (56.8%) received active treatment. Of this group, 1423 (65%) had potentially curable disease but only 627 actually received treatment with curative intent; this represented only 16.3% of all the patients evaluated. Surgical resection was undertaken in 411 (10.7%) and radiotherapy was administered to 1381 (35.8%) of all patients. However, high dose chest radiotherapy with curative intent was used in only 53 of 502 (10.6%) patients with localised disease that was not resected. The provision of combination chemotherapy was also low. In SCLC, for which it is regarded as standard therapy, only 425 of 678 cases (62.7%) were treated and, of these, more than half received single agent etoposide. Of the NSCLC cases only 8.2% received some form of chemotherapy. For all cases evaluated the median survival was 3.6 months with 21% of patients alive at 1 year and 7% at 3 years.

These findings should be considered within the context of the literature available in 1995 rather than what was available at the time of publication. For instance, the meta-analysis showing that chemotherapy for advanced NSCLC confers a survival advantage of 5% was not published until December 1995.14 Likewise, studies from the MRC and the London Lung Cancer Group showing that single agent oral etoposide resulted in poorer median survival and quality of life were not reported until 1996 and 1997 respectively.11 13 Unfortunately, many of the findings by Gregor and colleagues10 do reflect medical nihilism and the fragmented services and care pathways followed by these patients. It has been appreciated for many years that the most likely chance of cure from NSCLC is to undergo surgery. In this study the lung cancer resection rate was 11%, similar to the UK average for the same time period20 but less than half that quoted by studies from Holland, Italy and the US.21 23 Similarly, the low use of potentially curative high dose radiotherapy in patients with localised NSCLC who were not resected compares poorly with other countries where it is standard therapy.24 Although there is now some evidence that lung cancer patients in the UK have poorer performance status at initial presentation than in other countries, it is unlikely that this alone accounts for the disparity in treatment rates.21 Interestingly, patients managed by a clinician with a special interest in lung cancer were 16 times more likely to receive potentially curative treatment than those managed by other clinicians.17

Platinum based and non-platinum based chemotherapy in NSCLC

In 2001 the National Institute for Clinical Excellence (NICE) approved four new “third generation” drugs (paclitaxel, docetaxel, gemcitabine, and vinorelbine) for use against NSCLC in England and Wales.25 This decision was, in part, based upon a systematic review of available randomised controlled trials which suggested that these agents do confer a small benefit (2–4 months) in survival when compared with “best supportive care” or some of the older second generation agents.26 However, little work has been done to compare combinations of the new agents with platinum based chemotherapy regimens.

Georgoulas et al27 undertook a prospective randomised multicentre trial comparing the efficacy of cisplatin and docetaxel with that of gemcitabine and docetaxel in the treatment of advanced non-small cell lung cancer (second Introductory article). Cisplatin, which is now the mainstay of chemotherapy in NSCLC, is associated with significant toxicities whereas docetaxel and gemcitabine have milder non-overlapping toxicity profiles. Subjects had to be under 75 years of age, performance status 0–2, and have resectable stage IIIB or IV disease. The primary end point was a comparison of response rates and time to progression of the two regimes and secondary end points were toxicity profiles and overall survival. The study was designed as an intention to treat analysis with 80% power to detect a 12% improvement in the overall response rate with the cisplatin/docetaxel arm at a one sided 5% level of significance. The authors concluded that the cisplatin and docetaxel combination was equivalent to the gemcitabine and docetaxel regimen in terms of response rate, response duration, time to tumour progression, overall survival, and 1 and 2 year survival. However, the gemcitabine and docetaxel arm had the more favourable toxicity profile.

Although the results are potentially intriguing, there are a number of problems with the analysis. It was originally set up as an intention to treat study and 441 patients were randomly assigned to receive either docetaxel/cisplatin or gemcitabine/docetaxel. However, only 406 patients were actually evaluated. Despite being an intention to treat study, 35 patients were excluded after randomisation on the basis that they were either not treated, refused treatment, or had low performance status. Of the latter group, more were excluded from the gemcitabine/docetaxel arm (n=10) than from the cisplatin/docetaxel arm (n=4). Furthermore, the sample size was calculated on the basis of a one sided test, which is appropriate only when a result in the unexpected direction does not have an important meaning. Ideally, a two tailed test should have been considered. However, the major criticism of this study is that it is possible that, in designing their trial, Georgoulas and colleagues27 have overlooked a small but potentially important difference between the two treatment groups. The trial was designed as a difference trial to have 80% power to detect a 12% improvement in the overall response rate with the cisplatin/docetaxel regimen. These parameters were based on the results of phase II studies rather than reflecting differences that would have been important for the trial to detect. One of the interesting observations to come out of the recent meta-analyses of trials in NSCLC is that, with current chemotherapeutic agents, the survival benefits are of the order of only 5%. The meta-analyses were necessary because their constituent trials were, for the most part, too small to detect modest treatment effects reliably. It is possible that, if the present trial had been designed to detect an absolute 5% difference between the two groups, the results would have been different. However, in order to achieve this, several times the number of patients in each arm would have been required. One could therefore argue that this study was underpowered although it nevertheless makes a useful contribution to the literature.

Despite these problems, this study does raise the interesting possibility that a non-cisplatin containing regimen might have similar efficacy to a cisplatin containing one with the advantage of having a less toxic side effect profile. There may be a role for such agents in patients with co-morbidities that would otherwise prevent them receiving cisplatin containing regimens. Another somewhat unexpected finding was that patients with non-adenocarcinoma histology had a
significantly better response to cisplatin and docetaxel than patients with adenocarcinomas, and the inverse was seen for the gemcitabine/docetaxel regimen. The reasons for this are not immediately apparent and have not been noted previously. Before any conclusions are drawn as to whether adenocarcinoma and non-adenocarcinoma should be treated with different protocols, it should be remembered that, with advances in pathological diagnosis, it is now recognised that many lung cancers are chimeras rather than of single histology. However, this is an interesting observation and merits further investigation.

At this time the role of these “third generation” agents is still being evaluated and further large multicentre trials are required to try to answer some of the questions raised above.

Clinical implications

During the past 20 years medical and surgical intervention has resulted in little change in the long term survival for patients with lung cancer. The epidemic proportions of the disease are contrasted sharply with the general failure of conventional treatment. Some European countries are now reporting 5 year survival rates more than twice those in the UK, even though their resources are no greater and, in some cases, considerably less. What could the future therefore hold for the prevention and treatment of lung cancer in the UK?

Intensification of anti-smoking campaigns and screening for lung cancer

It is now established beyond any doubt that over 90% of lung cancers are caused by smoking. Preventing people commencing smoking and encouraging current smokers to quit must continue to play an important part in the strategy against lung cancer. Peto and colleagues have shown recently that people who stop smoking at 50 or 60 years of age avoid most of their subsequent risk of developing lung cancer and those who stop at 30 years of age avoid more than 90% of the risk attributable to tobacco of those who continue to smoke.23 Mortality rates from tobacco in the first half of this century will be affected far more by the number of adult smokers who stop than by the number of adolescents who start.

Two large studies have recently evaluated the efficacy of low dose computed tomographic (CT) scanning as a screening tool for lung cancer.24 25 Although both studies found that screening detected most cancers at an earlier stage (majority stage IA) than would be expected in an unscreened population, there was a high incidence of false positives.26 A recent report from a joint working party of the British Thoracic Society and the Society of Cardiothoracic Surgeons of Great Britain and Ireland has indicated that thoracic surgery is severely under resourced.27 At present there are a mere 40 pure thoracic surgeons in the UK and, because of the pressure of non-cancer surgery, lung cancer surgery comprises less than half of their workload. There is a call to double the number of thoracic surgeons in the UK and, of the number of thoracic surgeons is increased, there is evidence that they should be grouped in large centres rather than spread thinly around the country. A recent study has shown that patients who undergo surgery in hospitals which perform a high volume of lung cancer surgery have significantly higher 5 year survival rates and lower complication rates than those who undergo surgery in low volume units.41

The peak incidence of lung cancer in the UK is between 75 and 80 years of age. Patients over 65 years of age account for over 50% of lung cancer sufferers. However, Gregor et al found that patients aged under 60 were five times more likely to be given potentially curative treatment than those in the 70–79 age group and 33 times more likely than patients over 80.42 Other studies have shown that histological diagnosis rates are lower in elderly patients and that correct staging occurs less frequently.17 39 It has been shown previously that the survival of patients believed to have lung cancer, in whom the diagnosis is not histologically confirmed, is very poor.33 In their recent recommendations on flexible bronchoscopy, the British Thoracic Society states that it does not regard age as a contraindication and highlights several studies which have shown that elderly patients tolerate the procedure well.34 35 Similarly, there is no evidence that the elderly fare any worse when undergoing CT guided transthoracic fine needle aspiration biopsy.35 Although the prevalence of co-morbidity in patients over 70 years is higher, many have good or excellent performance status and the age related bias which has existed towards investigation and treatment in the past is no longer acceptable.

Brown et al36 found that the use of surgery or chemotherapy in patients with NSCLC aged under 65 was 18% and 21%, respectively, compared with 2.1% and 0% in those aged over 75 years. In SCLC 79% of those under 65 and 41% of those over 75 received chemotherapy. Age as a risk factor for lung cancer surgery is controversial, but the British Thoracic Society guidelines state that all patients should have equal access to lung cancer services regardless of age.38 The advent of video assisted thoracoscopic surgery (VATS) and limited surgical resection, although not widely practised at present, may have a significant role to play in staging and treatment of lung cancer, especially in the elderly population.39 Gregor et al40 showed that a thoracic surgeon involved in the management decision making process in only 10% of the cases reviewed in their study, irrespective of age. This is a reflection of the difficult time that thoracic surgery is currently experiencing in the UK; at present fewer than 10% of lung cancer cases are resected compared with resection rates of 24% and 25% in European and American patients.39 40 A recent report from a joint working party of the British Thoracic Society and the Society of Cardiothoracic Surgeons of Great Britain and Ireland has indicated that thoracic surgery is severely under resourced.41 At present there are a mere 40 pure thoracic surgeons in the UK and, because of the pressure of non-cancer surgery, lung cancer surgery comprises less than half of their workload. There is a call to double the number of thoracic surgeons in the UK, a target which will not be met for many years unless there is recruitment from overseas or surgeons are retrained from other specialties. However, although it is vital that the number of thoracic surgeons is increased, there is evidence that they should be grouped in large centres rather than spread thinly around the country. A recent study has shown that patients who undergo surgery in hospitals which perform a high volume of lung cancer surgery have significantly higher 5 year survival rates and lower complication rates than those who undergo surgery in low volume units.41

The low utilisation of chemotherapy for NSCLC in the study by Gregor et al40 reflects the scepticism for the benefit of chemotherapy in this tumour. Although the meta-analysis showing a survival benefit for those who had received chemotherapy was not published until the end of the study year, there remains a great deal of scepticism over
Learning points

Problems
- In the UK the 5 year survival for lung cancer is less than 5% compared with up to 14% in the US and some European countries.
- At present fewer than 10% of patients with lung cancer are resected in the UK compared with resection rates of up to 25% in Dutch and US patients.
- Despite studies showing the benefit of chemotherapy and radical radiotherapy for NSCLC, poor uptake of these treatment modalities in the UK is contributing to poor survival rates.
- Patients under 60 years are five times more likely to be given potentially curative treatment for lung cancer than those in the 70–79 age group and 33 times more likely than patients aged over 80 years.

Solutions
- Many elderly patients with lung cancer have very good performance status and the age related bias that has existed towards their investigation and treatment in the past is no longer acceptable.
- Rather than relying on meta-analyses to show survival benefits from large numbers of indeterminate trials, large carefully designed multicentre trials are required to assess the merits of new treatment regimens.
- All patients with lung cancer should be referred to a respiratory physician who has a specialist interest in lung cancer and these clinicians should coordinate the multidisciplinary team and take the lead in referring patients for definitive treatment.

chemotherapy for NSCLC even among respiratory physicians. The benefits are modest but such improvements could, given the high incidence of lung cancer, make a very considerable impact on median survival. Studies of patients' opinions of treatments for cancer have shown that many patients accept considerable toxicity in return for small improvements in survival. Medical nihilism may have more to do with the low utilisation of chemotherapy in NSCLC than patients' wishes. In a survey of 821 clinicians in the UK of whom 454 were directly involved in the care of lung cancer patients, two thirds reported that they would seek an improvement of more than 10% before adopting chemotherapy for NSCLC. Given the modest benefits shown by the meta-analyses, improvements of the order of magnitude of 10% are unlikely to be seen. The study by Georgoulias illustrates the statistical problems often seen with smaller studies and, while such results should not be ignored, they highlight areas that should be explored using large multicentre trials. After all, in the thrombolysis trials for acute myocardial infarction, it took tens of thousands of patients to show an absolute mortality benefit of about 3% in favour of thrombolytic therapy.

The British Thoracic Society has recently been conducting a randomised controlled trial to examine whether the addition of cisplatin based chemotherapy to standard treatment for NSCLC provides any significant improvement in survival—that is, it is attempting to address the same questions prospectively that the meta-analysis attempted to answer from retrospective data. If the results from this study support the meta-analysis findings, some of the clinicians who are currently “sitting on the fence” with regard to chemotherapy for NSCLC will hopefully be persuaded otherwise. Furthermore, if the new “third generation” chemotherapeutic agents are shown to have greater, or even similar, efficacy to the traditional cisplatin containing regimens as suggested by Georgoulias and colleagues, more clinicians may be persuaded to consider these new chemotherapeutic agents for their patients.

Organisation of lung cancer services
As a result of the Calman-Hine report there has been a review of the organisation of cancer services in England and Wales. Several sets of guidelines on the management of lung cancer patients have recently been published, and there is now a need for clinicians to implement them. At present there is a nationwide shortage of thoracic surgeons as well as radiation oncologists and respiratory physicians who have a special interest in lung cancer. To improve UK lung cancer survival and cure rates we need to increase dramatically the number of patients considered for active treatment. The development of multidisciplinary teams and improved access to lung cancer specialists through the development of clinical networks should increase the percentage of patients—particularly elderly patients—seeing a specialist and therefore being considered for active treatment. One recent assessment of the proportion of patients with NSCLC who should be considered for chemotherapy at some stage in their illness put the figure at about 50%. Gregor's study also indicated that only 2.9% of lung cancer patients in Scotland in 1995 participated in a clinical trial. This is a woefully inadequate figure given the multitude of questions that remain to be answered with regard to best practice for lung cancer. The recent meta-analyses have clearly shown that chemotherapy survival benefits are marginal and therefore large numbers of patients need to be recruited in order to attain sufficient power to demonstrate this. Rather than relying on...
meta-analyses to show survival benefits, we should be aiming to undertake carefully designed multicentre trials designed to answer certain key questions. The Big Lung Trial, the results of which are eagerly awaited, is one of the first attempts to do this for lung cancer in the UK. There is certainly no shortage of lung cancer patients in the UK and it could be argued that all patients should be considered for a trial whether they are receiving active treatment or standard palliative care.

Most patients with lung cancer in the UK present to, are diagnosed by, and are managed at least in part by respiratory physicians. The study by Gregor et al clearly showed that patients fared better if they were managed by a clinician (respiratory physician or oncologist) who has a special interest in lung cancer. This trend has been noted before and appears to be due to the fact that thoracic physicians refer more patients for surgical and oncological opinions. There is therefore now a strong case for all patients with lung cancer to be referred, in the first instance, to a respiratory physician who has a specific interest in lung cancer and these clinicians should coordinate the multidisciplinary team. This type of approach should optimise and focus patient investigation and management and, if all lung cancer clinicians take a proactive stance, we should begin to see an improvement in lung cancer survival and cure rates in the UK.

Acknowledgements

We are grateful to Dr R Prescott of the Department of Public Health Sciences, University of Edinburgh Medical School for comments on the manuscript.

References


