Therapies in Metastatic Non-small-cell Lung Carcinoma

a report by

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Lung cancer is the most common killing cancer in men and women in the Western world. Eighty per cent of cases are non-small-cell lung carcinoma (NSCLC), whose subtypes include squamous cell carcinoma, adenocarcinoma and large-cell carcinoma. Of these, approximately 80% will present with either locally advanced or metastatic disease, i.e. stage IIIB or IV disease, and are unlikely to be cured.

Treatment options for these patients include best supportive care (BSC), chemotherapy or a combination of radiotherapy and chemotherapy. NSCLC is less chemosensitive than small-cell carcinoma and complete responses are rare, but nevertheless chemotherapy provides some improvements in quality of life (QOL) and life expectancy compared with BSC, particularly in better performance status (PS) patients. This article will discuss the medical treatment of NSCLC and briefly consider the newer epidermal growth factor receptor (EGFR) antagonists.

Chemotherapy versus Best Supportive Care

Chemotherapy became a serious entity for NSCLC only in the mid-1990s, particularly after a meta-analysis by the NSCLC Collaborative Group that looked at all randomised controlled trials (RCTs) of chemotherapy or BSC in all treatment situations, i.e. surgery, radiotherapy or BSC.[1] In trials of chemotherapy versus BSC in advanced disease, nine RCTs showed that chemotherapy conferred a small survival advantage of six to eight weeks. However, in these retrospective analyses there were no QOL data and chemotherapy regimes may have considerable side effects, both of which are important to take into account. Inevitably, there will be a balance between the effects of chemotherapy and response on QOL, which may be balanced by any additional morbidity of these regimes. After chemotherapy, the overall one-year survival rate in advanced disease was 30% compared with only 17% after BSC.

Chemotherapy Regimens

The NSCLC Collaborative Group meta-analysis showed that only cisplatin-containing regimens were effective, but the advantages were small.[1] Although a number of different regimens of these second-generation compounds have been used, there is little to choose between them; however, several drugs in combination were better than single-agent therapy, with better response rates and prolonged survival at the cost of increased toxicity with combination therapy. Common second-generation chemotherapy regimens include mitomycin, ifosfamide and cisplatin (MIC) and mitomycin, vinblastine and cisplatin (MVP). The effect of MIC versus BSC was studied by Cullen in 351 patients, demonstrating a prolongation in median survival of seven weeks.[2] Smith et al. studied the effect of another common regime and in particular the duration of chemotherapy by administering either three or six cycles of MVP.[3] The authors concluded that there was no benefit in continuing chemotherapy beyond three cycles in terms of median survival, one-year survival and QOL. These regimes were used in over 70% of the patients in the Big Lung Trial that compared BSC with four different chemotherapy regimes. Importantly, it demonstrated a survival benefit with no detrimental effect in terms of QOL for the addition of chemotherapy.[4]

This advantage had previously been hinted at, for example by Cullen et al., who compared four courses of MIC with BSC and demonstrated an increase in median survival of two months. The overall response rate to chemotherapy was 31%, with a complete response of 2% and a partial response of 29%. Only a small subset of patients entered a QOL study and this showed an improvement in the symptom scores as measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Lung Cancer (QLC-LC) module 13. However, the largest study of this type was the Big Lung Trial, with nearly 400 patients recording QOL.

Over the last decade, new drugs have emerged including gemcitabine, vinorelbine and the taxols. These third-generation agents are more expensive, but have the advantage of better tolerance and they can be given as outpatient treatment. However, once again there was little to choose between regimens such as carboplatin/gemcitabine, carboplatin/vinorelbine or carboplatin/paclitaxel, with approximately a

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nine- to 10-month median survival and an increase to 35–40% of patients alive at one year.[6] Also, docetaxel has emerged as an effective single agent, with 15–20% responding when used as second-line treatment at relapse.[6]

In the UK, carboplatin/gemcitabine has become the favoured first-line treatment following the study of Rudd et al., which compared gemcitabine and carboplatin (GC) with the older regimen of MIC.[7] GC conferred a median survival of 10 months compared with a median survival of 7.6 months for MIC, with one-year survival rates of 40 and 30%, respectively. The response rates were similar for the two regimes: GC 42%, and 41% for MIC. GC had fewer side effects and resulted in fewer hospital admissions, and there was a highly significant advantage for most QOL variables studied for the newer regimen.

Chemotherapy in Elderly Patients

The mean age at presentation with lung cancer in the UK is 68 years, with 40% of patients presenting at 70 years of age or above. Most of the phase III RCTs tend to recruit younger patients, with just 10% being over 70 years of age. Hence, prospective data on the tolerance and responses seen by the elderly tend to be retrospective data from large trials that did not specifically set out to determine how the elderly would fare with chemotherapy. It is clear that more elderly patients either refuse or are not offered chemotherapy.[8] In 2000, Earle et al. showed that only 22% of patients over 65 years of age received chemotherapy, and the Surveillance Epidemiology and End Results (SEER) data from the US (collected between 1988 and 1995) showed that only 32% of patients over 65 years of age received chemotherapy.[9]

There have been some specific trials of chemotherapy in elderly patients with NSCLC. Langer et al. studied the effects of three different regimes: cisplatin/etoposide, high-dose paclitaxel/cisplatin and low-dose paclitaxel/cisplatin.[10] The two taxol arms had a better response, with the median survival being 10 and 9.5 months in the taxol arms versus 7.6 months in the non-taxol arm. QOL changes were similar to studies in younger patients. Although the response rate, toxicity and survival were similar to those in younger patients, there was more co-morbidity, leukopenia and neuropsychiatric toxicity in the older patients. The Italian lung cancer in the elderly study (MILES) study examined the effect of combination chemotherapy versus single-agent vinorelbine.[11] Six hundred and ninety-eight patients were entered and demonstrated that combination chemotherapy did not provide any survival benefit compared with vinorelbine alone.[12] However, Frasci et al. showed that combination therapy produced a superior median survival, although the chemotherapy doses used were different in the two studies, which made it difficult to compare results.

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The (Elderly) Lung Cancer Vinorelbine Italian Study (ELVIS) compared vinorelbine as a single agent with BSC.[13] Although, the study was terminated early due to poor recruitment, in the 191 patients a prolongation in median survival of seven weeks was demonstrated with chemotherapy. Patients who received vinorelbine performed better on functional assessments, but scored worse on toxicity. These studies were performed on patients with a PS of 1 or 2; however, the majority of patients had a PS of 1. In general, good PS patients tolerate and respond better to the chemotherapy. However, some PS 2 patients can also do well, but in general they suffer more toxicity than those with PS 0–1 and the progression-free interval is shorter.

> There has been a lot of interest as to whether a combination of radiotherapy and chemotherapy provides an additional survival benefit in locally advanced non-small-cell lung carcinoma.

Trials of chemotherapy in elderly patients have given conflicting results with better median survivals than with BSC, and with a suggestion that single-agent chemotherapy may be less toxic than combination therapy and confers a small survival benefit.[14]

Chemotherapy and Radiotherapy

Local radiotherapy is a useful tool in the palliation of lung cancer. Radical radiotherapy is used in the treatment of stage IIIA and IIIB disease, and most studies report a median survival of eight to 12 months. There has been a lot of interest as to whether a combination of radiotherapy and chemotherapy provides an additional survival benefit in locally advanced NSCLC. Many trials have looked at this question.[1] A meta-analysis by the NSCLC collaborative group that looked at 22 RCTs including 3,033 patients compared patients randomised to have chemotherapy alone versus those receiving combination chemotherapy and radiotherapy. The patients who received combination treatment demonstrated a prolongation in their median survival of seven to eight weeks.[15] Furuse et al. took this matter further to determine whether concurrent chemoradiotherapy or sequential chemotherapy and radiotherapy is more advantageous. Patients were randomised to receive either concurrent therapy with mitomycin, vindesine, cisplatin and radiotherapy or sequential chemotherapy and radiotherapy. Concurrent chemo-radiotherapy significantly enhanced median survival (16.5 versus 13.3 months). Trials are ongoing concerning the timing of chemotherapy and radiotherapy in NSCLC.

Non-small-cell Lung Carcinoma and Performance Status

PS is an independent prognostic factor, and patients with a PS of 2 demonstrate lower response rates to chemotherapy and shorter time to treatment failure, have higher toxicity and tolerate fewer courses of chemotherapy. Many trials have looked at the effects of chemotherapy versus BSC. The trials all used different chemotherapy regimes; however, current consensus opinion is to use single-agent therapy with gemcitabine, vinorelibine or a taxane. The alternative regime is carboplatin-based combination chemotherapy.

Epidermal Growth Factor Receptor Inhibitors

EGFR has been demonstrated on the cell surface of 60–90% of NSCLCs. Downstream pathways stimulated by EGFR phosphorylatin result in cancer cell proliferation and inhibition of apoptosis, among other things, and drugs have been developed that block this receptor. Gefitinib was the first agent developed. The mechanism of action of gefitinib is to block EGFR tyrosine kinases, which reduce cell proliferation.[16,17] The 'Iressa' Dose Evaluation in Advanced Lung Cancer (IDEAL 1 and 2) trials administered gefitininb at 250 and 500mg; however, there was no placebo arm in these studies. Gefitinib was given to patients who had been previously treated with two or more chemotherapy regimes and had relapsed. There were approximately 200 patients in each trial. Symptom improvement occurred in both treatment groups and differences between the two doses were not significantly different. The radiographic response rate was also similar between the two dosing groups, with a partial response rate of 13 and 9% in the 250 and 500mg groups respectively, although it was generally lower in more heavily pre-treated patients. These uncontrolled studies led to the launch of gefitinib for general use in pre-treated patients at relapse.

However, the larger Iressa Survival Evaluation in Lung (ISEL) cancer trial, which compared gefitinib at relapse with placebo in more than 1,600 patients, showed no survival benefit for the addition of gefitinib.[18] However, a subgroup analysis showed a survival benefit in Asian patients, females, non-smokers and the adenocarcinoma cell type. Another mode of timing was studied, where gefitinib was randomised to be given at the beginning of treatment with a platinum-based regimen of either cisplatin and gemcitabine or carboplatin and paclitaxel.[19] This trial demonstrated no benefit in terms of median survival, time to progression, response rate or overall survival by the addition of these drugs to standard chemotherapy regimes.

Shepherd et al. performed a large RCT in relapsed advanced NSCLC with another EGFR inhibitor, erlotinib.[20] It was used in patients who had one or two previous chemotherapy regimes and included a placebo arm. This study demonstrated a prolonged median survival of two months with erlotinib compared with placebo, and 31% of patients were alive at one year in comparison with 22% in the placebo arm. Interestingly, multivariate analysis again demonstrated that Asian origin, female gender and non-smokers were independent variables for better survival with erlotinib. Analysis of the histological subtype identified that patients with adenocarcinoma were more likely to have a benefit. Thus, current evidence shows that the use of these agents in combination with first-line chemotherapy is not beneficial, but in relapsed disease these agents provide a median survival advantage of up to eight weeks. Research is now attempting to predict those patients who are most likely to respond to these agents and why, so that they may receive truly targeted therapy – a claim that seems premature at present.

Developments in targeted therapy may be increasingly important in the future, as chemotherapy seems to have reached a plateau.

Conclusion

A number of chemotherapy agents demonstrate activity in NSCLC. There are several regimes available, although no regimen stands out. Third-generation combination chemotherapy achieves a 30–40% partial response rate and prolongs median survival by three to four months compared with BSC, with about 35% of patients alive at one year. Modern chemotherapy has fewer toxic effects compared with the older regimens of the early 1990s. Developments in targeted therapy may be increasingly important in the future, as chemotherapy seems to have reached a plateau. ■

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