Progress in the Treatment of Advanced Non-small Cell Lung Cancer

a report by
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Lung cancer continues to be the leading cause of cancer-related deaths in both men and women, with the main culprit being tobacco. Major changes have been observed in the global epidemiology pattern within the last decade, with an increased cigarette consumption, especially of 'light' filter cigarettes among females in most countries, while the consumption is levelling off in males in some countries – but, unfortunately, not in heavily populated areas, such as China, India and Russia, etc.

At the same time, the composition of cigarettes has changed with less tar and nicotine but increased levels of nitrosamines – well-known strong carcinogenes. These changes have resulted in a marked increase of adenocarcinomas, which are usually located peripherally in the lung, while a decrease has been noted for both small cell lung cancer and epidermoid carcinoma, which are usually more centrally located.

The management of lung cancer has also undergone major changes during the last decade and, although increasingly complex, it is also characterised by therapeutic optimism, particularly among non-small cell lung cancer (NSCLC, comprising epidermoid, adeno- and large cell carcinomas), which accounts for approximately 80% of all lung cancers.

Surgery is considered the curative treatment of NSCLC, but, unfortunately, only 15% to 20% of these tumours can be radically resected and, overall, survival of surgically treated patients is only approximately 40% at five years.

Some, if only modest, improvement has occurred within recent years, with the addition of chemotherapy as an adjuvant to surgery in radically resected patients. However, the majority of NSCLC patients present with advanced disease at diagnosis and a large part of those diagnosed with early stage disease eventually recur, experiencing metastatic disease. For advanced disease, palliation and the patient's quality of life are still the primary goals of therapy, with total cure remaining elusive.

Until recently, pneumologists have generally taken a nihilistic view of chemotherapy for the treatment of advanced lung cancer. This view has, however, changed in recent years thanks to the development of new cytostatic agents as well as the emergence of targeted therapy based on the major advances in the knowledge of tumour biology and mechanisms of the oncogenics of lung cancer.

With respect to cytostatic agents, the most active agents are shown in *Table 1*. Standard therapy for patients with advanced NSCLC is cytotoxic chemotherapy and numerous trials have shown that chemotherapy can improve survival, enhance quality of life and be cost-effective.

Older studies have clearly demonstrated that a cisplatin-doublet produces a survival advantage over single agents and recent studies have indicated that other two-drug combinations, excluding platinum compounds, also show a similar activity as platinum-containing regimens.

Currently, no studies have shown that a three-drug combination is superior to a two-drug combination. Median survival for patients with advanced disease and good performance status is usually approximately 10 months, with one-year survival of 35% to 45%. Objective response is usually noted in one-third of patients and symptomatic improvement in more than 50% of those treated. The duration of treatment is usually four months. Elderly patients and patients with poor performance status also benefit from cytostatic treatment with two-drug combinations, with results quite similar to the treatment of younger patients.

When patients relapse, second-line therapy with docetaxel is usually considered the standard of care, with a 7% objective response rate and a seven-month median survival in randomised trials. Other drugs have also shown activity in randomised trials, however, and most recently a new experimental agent, pemetrexed (Alimta® – a novel multitargeted antifolate), was compared with docetaxel. In this trial, response rate, median survival and overall

survival were similar in the two arms and the toxicity pattern favoured the pemetrexed arm with significantly less neutopaenia.

With respect to targeted therapies in advanced lung cancer, the epidermoid growth factor inhibitors are at the forefront of promising agents and the only ones hitherto tested in randomised trials. Gefitinib (Iressa®) was the first one to undergo extensive clinical testing, both as a single agent and when combined with chemotherapy. Gefitinib results in symptomatic improvement in 30% to 40% of all patients and particular benefit has been observed among females with adenocarcinoma who have never smoked.

In the latter highly selected group, the response rate increased from 60% to 70% and a particular high activity was noted in patients with the subtype 'broncho-alveolar cell carcinoma'. Gefitinib, and also the other epidermal growth factor (EGF) inhibitor erlotinib (Tarceva®), failed to demonstrate improvement in survival when combined with two different chemotherapy regimens. Recent data, however, have indicated that Tarceva results in improved survival as salvage treatment when used as a single agent, compared with placebo in patients with advanced NSCLC, either as second- or third-line treatment, with median survival being 6.7% months for Tarceva and 4.7% months for placebo, respectively. Again, the highest activity has been observed among East Asians and females with adenocarcinoma who have never smoked.

The explanation of the lack of additive or synergic activity of EGF inhibitors and chemotherapy in first-line treatment of advanced NSCLC is still puzzling. A number of molecular studies, including the use of immunohistochemistry and of FISH-analysis, on tumour tissue with determination of EGF receptors, including gene mutation analysis, are on-going in order to shed more light on these aspects and hopefully thereby also enable the determination of the clinical likelihood of achieving response to EGF inhibitors in the individual patient. Both drugs have the advantage of being given orally with few side effects compared with classical cytostatic agents.

The most recent advancement in the treatment of advanced non-small cell lung cancer was presented at the latest meeting of the American Society of Clinical Oncology annual meeting in June 2005. The addition of bevacizumab (Avastin®), an inhibitor of vascular endothelial growth factor (VEGF), to platinum-based chemotherapy (paclitaxel and carboplatin) significantly improved overall survival by more than 20% in a study involving 434 patients who received bevacizumab compared with 444 patients who only received the chemotherapy (median survival 12.5 months versus 10.2 months). The improved response rate (27% versus 10%) and a longer time to progression (6.4 months versus 4.5 months) were observed in the bevacimab group. Of note, the study excluded patients with squamous cell histology because previous studies have found a serious risk of life-threatening bleeding, particularly among those with squamous cell carcinoma.

Clinically meaningful advances have, therefore, already been achieved by the use of targeted therapy, with EGF receptor tyrosine-kinase inhibitors giving a further chance of tumour control and/or symptom palliation in a subset of patients otherwise only eligible for supportive care.

It is hoped that additional advances in the future will be seen, both with respect to optimising the use of the previously mentioned agents in combination with classical therapies, such as surgery, radiotherapy and combination chemotherapy, but also based on the many on-going trials exploring the efficacy of all the other types of targeted treatments of NSCLC (see *Table 2*). For the first time in decades a more optimistic viewpoint can be taken concerning survival and quality of life in patients with advanced NSCLC. ■

Table 1: Frequently Used Active Agents in Combination Chemotherapy

Alkylating agents	
	Cisplatin
	Carboplatin
	Ifosfamide
Antimitotic agents	
	Docetaxel
	Paclitaxel
	Vinblastine
	Vinorelbine
Antimetabolites	
	Gemcitabine
Topiosomerase inhibitors	
	Etoposide
	Mitomycin
	Irinotecan

Table 2: Targeted Therapy in Non-small Cell Lung Cancer

Epidermoid growth factor family inhibitors
Angiogenesis inhibitors
Signal transduction inhibitors
Apoptosis inducers
Cancer vaccines
Gene therapy