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Non-small Cell Lung Cancer: An Overview of Current Management

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Non-small cell lung cancer (NSCLC) will remain a worldwide health problem for the foreseeable future. Unfortunately, local treatment of this disease is disappointing as most patients develop uncontrollable locally advanced or distant metastatic disease. The recent meta-analysis using updated patient data has suggested a potential role for adjuvant cisplatin-based chemotherapy (CT) in early stage disease, and has shown a significant, albeit modest, improvement in survival when combined with radiotherapy in locally advanced disease and as a single modality in metastatic disease. Although quality and cost of extra life with this more aggressive treatment need to be defined in prospective studies, CT should be considered standard treatment for patients with locally advanced and metastatic NSCLC able to receive cisplatin-based CT. Its role in stage I and II disease is under current investigation. Ongoing clinical studies with more active agents, novel combined modality treatment strategies and laboratory discoveries continue to emerge which may lead to valuable new treatment options to extend this survival advantage. © **1997 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

LUNG CANCER remains the major cause of cancer-related death in North America and Europe and its incidence is likely to increase in developing countries because of the rise in tobacco consumption [1–3]. Thus, it will remain a major health problem worldwide in the forthcoming decades. Approximately 75% of lung cancer is non-small cell carcinoma (NSCLC) which comprises several histological types: squamous cell, adenocarcinoma and large cell carcinoma. Approximately 70% of patients with NSCLC present with unresectable disease. These patients are incurable with conventional treatment and are candidates for palliative radiotherapy (RT) and/or chemotherapy (CT) [4]. Of the 30% who have surgery, only one-third are alive at 5 years [5, 6]. Therefore, as most patients present with, or subsequently develop uncontrollable disease, the overall prognosis is poor with < 10% surviving long-term [7].

Aetiology

Smoking, exposure to environmental smoke, as well as occupational exposure to radon, and beryllium are all known risk factors for developing lung cancer [8–11]. Increased risk has been reported for copper miners and stainless steel foundry workers [12, 13]. However, tobacco consumption is the most clearly defined risk factor for the development of lung cancer and is implicated in 85% of lung cancer deaths [9]. When assessed by histological type, an estimated 95% of squamous cell, 85% of large cell and 70% of adenocarcinoma are tobacco-associated [5]. Risk increases with increased daily consumption and duration [14, 15]. Tobacco consumption by males has declined in recent years but has increased in women and adolescents. Unfortunately, there is little evidence that current prevention programmes will have a major impact on the incidence of lung cancer in the coming years.

Although risk factors have been known for decades, it is only recently that some of the molecular events leading to carcinogenesis have been elucidated. Abnormalities of proto oncogenes and tumour suppressor genes have been described in virtually every type of cancer including NSCLC [16–19]. History of heavy tobacco consumption is associated with *K-RAS* mutations, usually G to T transversions, and these are associated with poor prognosis [20–23]. Abnormalities of *P53* are the most common genetic aberrations in lung cancer [24–27]; however, interstitial or terminal deletions of chromosome 3p, loss of *MCC* or *APC* putative suppressor genes at 5p21 locus, and cytogenetic abnormalities at 9p have all been reported in NSCLC specimens [16]. Abnormal expression of *P53* and *BCL-2* and loss of *RB* are also associated with reduced survival. Interestingly, both abnormal *P53* expression and 3p-abnormalities have been found in samples of dysplastic epithelium adjacent to malignant cells [17]. Whether premalignant lesions in bronchial mucosa contain detectable genetic lesions that may prove useful in the early detection of lung cancer in high risk patients or whether abnormalities of *P53* and *K-RAS* are amenable to manipulation by gene therapy remain areas of intensive research [28–32].

Prognosis and treatment of NSCLC

Early stage disease. Surgical cure is only achieved in patients with early stage disease. The 5-year survival rate of patients is

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approximately 70% with stage I, 30% with stage II and 10–20% with stage III disease [6, 7]. New surgical techniques and improvements in supportive care have reduced postoperative morbidity and mortality. However, surgery alone will not substantially increase survival as most patients with clinically resectable disease have micrometastases at presentation which cannot be eradicated by local therapy alone. Previously, adjuvant RT and/or CT did not appear to influence the natural history of early stage NSCLC. The recently published meta-analysis, using updated patient data, suggests that adjuvant cisplatin-based CT is associated with a relative reduction in risk of dying of 13% or an absolute improvement in 5-year survival of 5% ($P = 0.08$, CI:1–10%) [33]. Although the results of this subset analysis were not statistically significant, confirmation of the potential benefit of adjuvant CT is being sought through ongoing large multicentre, multinational trials. The role of pre-operative CT in early stage disease is being investigated in an ongoing French phase III study.

Locally advanced resectable disease—(stage IIIA). The use of pre-operative CT for locally advanced disease may become the most significant development in the management of NSCLC for many years. There are several potential theoretical benefits from this approach, including control of systemic disease before the development of resistance, improved delivery of CT to tumour cells before alteration of tumour vasculature from surgical manipulation, continuation of a regimen proven to be effective after pathological examination of the resected specimen, and facilitation of complete resection if tumour regression occurs. Almost all pilot studies have shown an overall response rate of > 50%. Approximately 70% of patients on these trials were offered surgery, and complete resection was possible in 60%, although only a few have achieved pathological complete response rates of 10–15%. Median survival ranged from 8 to 31 months, with 2–3 year survival rates of approximately 30% [34, 35]. Three randomised trials examining the benefit of pre-operative CT have been instituted recently and provocative results are available. The regimens used were mitomycin C with ifosfamide and cisplatin; cyclophosphamide with etoposide and cisplatin; and etoposide with cisplatin. These were compared with either surgery alone or combined with RT [36, 37]. Interim analyses in two studies showed significant survival benefits for the pre-operative CT arms (median survivals: 26 versus 8 months and 64 versus 11 months), leading to premature closures of the studies [36, 37]. The third trial showed a trend toward improved median survival (28.7 versus 15.6 months) [38]. The magnitude of the improvement with combined modality therapy is not entirely consistent with previous data and, given the small numbers of enrolled patients at the time these studies were closed, early termination might have biased estimates of the treatment effect. However, the results are interesting and provide a strong rationale for continuing to examine pre-operative therapy for patients with locally advanced NSCLC.

Locally advanced unresectable disease—(stage IIIB). Traditionally, locally advanced NSCLC has been treated solely with RT. Although RT can ameliorate symptoms and extend survival in a proportion of patients, long-term results are poor with only 5% of patients surviving 5 years. The limited benefit of RT is not surprising as these tumours tend to spread early in their natural history and most patients die with local regional and systemic metastases. Although the evaluation of CT in NSCLC dates back to the early 1970s, it was only with the demonstration of the activity of cisplatin in the early 1980s that the modern era of CT investigation in NSCLC began. There have been 12 randomised trials testing the addition of cisplatin-based combination CT to radiotherapy (CRT) [33, 39–50]. Three of these trials have demonstrated a significant survival benefit [33, 39–49]. The CALGB study of cisplatin and vinblastine followed by RT compared with RT alone, in patients with excellent performance status and without supraclavicular adenopathy, has recently been updated [46, 47]. Median, 1-year and 5-year survivals are as follows: 13.7 versus 9.6 months, 54% versus 40% and 19% versus 7%. The French study, CEBI 138, randomised patients between six courses of a four-drug regimen of vindesine, lomustine, cyclophosphamide and cisplatin with RT compared with RT alone. At a mean follow-up of 61 months, patients randomised to CRT had a significant improvement in rate of development of distant metastases and survival [48, 49]. The percentages of patients alive at 1, 2 and 5 years were 41%, 14%, 3% for RT, and 51%, 21%, 6% for CRT, respectively. These results are consistent with those of the recent RTOG/ECOG three-arm trial which showed that survival was superior with induction cisplatin and vinblastine and conventional RT compared with either conventional or hyperfractionated RT alone [50].

Trials using concurrent CT and RT have yielded mixed results. Only 1 or 2 randomised trials testing single-agent cisplatin have reported a survival benefit [51, 52]. In an EORTC trial, split course RT was compared with RT and concurrent cisplatin administered either daily or weekly [51]. Patients who received RT and daily cisplatin had a statistically significant improvement in survival at 3 years compared with those who received RT (16% versus 2%). The time development of distant metastases was not significantly different between the groups; however, the group who received daily cisplatin had a marked improvement in survival without local recurrence, supporting the use of cisplatin as a radiosensitising agent.

It is not surprising that only a few studies have shown a statistically significant benefit with CRT over RT alone since 8 of the trials evaluating cisplatin-based CT randomised fewer than 150 patients. The recently published meta-analysis using updated patient data from 22 trials involving 3033 patients showed a statistically significant benefit for CRT compared to RT [33]. The subset of 11 trials using cisplatin-based CT provided the strongest evidence for an effect favouring CRT. The hazard ratio (HR) of 0.87 corresponds to an absolute benefit of 4% at 2 years and 2% at 5 years ($P = 0.005$). Treatment effect was consistent regardless of age, sex, histology, performance status or stage. Based on the results of the meta-analysis, CRT provides improvement, albeit modest, in survival. Although quality and cost of extra life with this more aggressive treatment need to be defined in prospective studies, CRT should be considered standard treatment for patients with locally advanced NSCLC able to receive cisplatin-based CT. Optimisation of combination CT and RT regimens, timing of the modalities and the use of radiosensitising agents are areas requiring further development.

Metastatic disease. After > 30 years of clinical research, there is little consensus on the optimal combination CT regimen for metastatic NSCLC. Methodological inconsistency amongst clinical trials and, more importantly, the lack of highly effective CT have contributed to this confusion. In general, responses have been observed in < 50% of patients and complete remissions are unusual. Once again, the meta-analysis demonstrated a modest impact of cisplatin-based combination CT on

survival compared with supportive care. The hazard ratio of 0.73 corresponds to a relative reduction in risk of death of 27% ($P < 0.0001$), or an absolute improvement in survival at 1 year of 10% and an improvement in median survival of 1.5 months [33]. Unfortunately, this analysis did not identify which drugs should be combined with cisplatin to achieve the optimal effect. Direct comparisons between cisplatin-based regimens with various vinca alkaloids and etoposide have failed to yield clear answers [53–61]. Vindesine was compared with vinblastine in combination with cisplatin and the results indicated a non-significant trend towards a higher response rate in the vinblastine arm and towards longer duration of response for the vindesine combination. Severe leucopenia was more frequent in the vinblastine arm [56]. Four studies have shown that vindesine with cisplatin is as active as etoposide with cisplatin in terms of response rate and survival, although it was associated with more frequent granulocytopenia and peripheral neuropathy [57–60]. In a recently reported, well-designed three-arm study comparing cisplatin and either vinorelbine or vindesine with single-agent vinorelbine, both higher response rate and longer survival were observed with vinorelbine and cisplatin compared with vindesine and cisplatin (median survival duration, 40 versus 32 weeks, $P = 0.04$; median response rate 30% versus 19% $P = 0.02$) [61]. There was a significantly higher incidence of grade 3 and 4 neutropenia in the vinorelbine arm while severe neurotoxicity was more common with the combination of vindesine and cisplatin. Based on the results of phase III trials to date, cisplatin in combination with either a vinca alkaloid or etoposide should be considered for patients able to receive cisplatin-based CT.

New drugs. Although virtually every known cytotoxic agent has been tested for efficacy against NSCLC, historically only cisplatin, vinca alkaloids, mitomycin C and ifosfamide have been associated with response rates consistently > 15% [4]. It is not surprising that this limited activity has produced only marginal benefits. After a paucity of new developments in the 1980s, six agents have now entered advanced clinical investigation in the 1990s. Many have novel mechanisms of cytotoxicity and offer promising activity against this chemoresistant tumour. New agents include camptothecin analogues, irinotecan (CPT-11) and topotecan [62, 63], the nucleoside analogue, gemcitabine [64, 65], the taxoids, paclitaxel and docetaxel [66–69], and the new vinca alkaloid, vinorelbine [61, 70, 71]. All have single-agent activity of over 20% against NSCLC. Several have toxicities related to myelosuppression, and possible dose–response relationships are being investigated. Most are being tested in combinations, particularly with cisplatin, with promising results, and randomised trials should provide additional information on their role in the treatment of NSCLC. RT in combination with taxoids, camptothecin analogues and gemcitabine, all of which have been shown to be radiation sensitisers, could be of particular importance in the future management of locally advanced disease.

Quality of life and cost effectiveness. The meta-analysis has shown that CT does improve survival in NSCLC, but it does not provide information on the cost and quality of extra life. Over the last 20 years there has been a growing consensus among health care providers and researchers that efficacy of therapeutic interventions should be evaluated by their impact on both quality and quantity of life [72–74]. This interest in measuring quality of life reflects an awareness that increasingly complex interventions are resulting in marginal benefits in survival, the trend toward a holistic, patient-orientated approach to health, and a growing recognition of the limitations and thus dissatisfaction with traditional assessments of well-being which focus on physical signs/symptoms of disease and toxicity of treatment [73, 74]. For example, the strongest predictor for survival is performance status (PS) [75], however, the meta-analysis suggests that PS does not predict for improved survival with treatment. There is evidence that patients with poor performance status are also those who are most likely to experience treatment-related toxicity rendering therapeutic decisions in this group of patients difficult [59]. It is also recognized that higher response rates do not necessarily correlate with improved survival nor does lack of response correlate with lack of symptom palliation [76, 77]. Hopefully, the inclusion of quality of life (QOL) endpoints with the more traditional outcome measures of toxicity, tumour response and survival in clinical trials offers a more comprehensive approach to monitoring the effects of therapy and to evaluating the relative risks and benefits associated with treatment.

Unfortunately, measurement of QOL in patients in NSCLC has been hampered by methodoligical problems; specifically, the lack of validated instruments, the lack of compliance with administering and collecting completed questionnaires and the difficulty in determining the clinical relevance of statistically significant changes in QOL scores. The first problem has been addressed and there are now several instruments that are valid, reliable and sufficiently brief to be of practical use in clinical trials. These include: the Functional Assessment of Cancer Therapy (FACT), the Lung Cancer Symptom Scale (LCSC), the European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ C30) and the Quality of Life Index (QLI) [78–81]. The results from therapeutic trials using these questionnaires are awaited with interest.

Incomplete data collection has been more difficult to overcome. As patients become more ill they are unable to fill in questionnaires. As time passes, QOL scores tend to become artificially inflated because the sickest patients are no longer included in the follow-up evaluations. Methods are being devised to compensate for this problem, but at present QOL analyses which have a high percentage of missing data must be viewed cautiously [82]. Determining the clinical relevance of QOL scores is also problematic: emphasis on documenting improvement in QOL with therapy may not be appropriate. Patients who enter clinical trials often have good performance status with minimal symptoms and may well rate their QOL quite high. In this setting it would be difficult to show improvement in QOL and stability, or slowing of the rate of decline in QOL may be a more meaningful outcome. Finally, although instruments detect statistically significant differences of changes in QOL over time between treatments, the clinical relevance of these measured changes and the manner in which QOL results should impact on therapeutic decisions needs to be clarified through continued study.

For the reasons cited above, published results to date do not definitively demonstrate the benefits or detriments of CT on QOL of NSCLC patients. Several studies in both NSCLC and small cell lung cancer (SCLC) suggest that psychosocial well-being more closely parallels disease-related symptoms than treatment-related symptoms. There are studies which suggest that anticancer therapy can improve disease-related symptoms, and there have been significant improvements in eliminating treatment-related toxicities [76, 77, 82]. There is also evidence to suggest that clinical staff generally require higher thresholds of potential benefits to offer treatment than patients require to

accept it [83]. Patients may well be willing to tolerate treatment to obtain modest improvements in survival. In the absence of data from clinical trials which can be generalised to the individual, the assessment of the risks and benefits of CT is best left with patients and their clinicians.

In the current era of rising health care costs and shrinking budgets, much greater interest is being placed on determining the cost and cost effectiveness of new interventions. The few published studies to date suggest that CT for advanced NSCLC is cost effective. In a Canadian randomised trial of CT versus supportive care for advanced NSCLC, treatment with cyclophosphamide, doxorubicin and cisplatin was less costly than supportive care, presumably related to fewer complications and hospital admissions [84]. More recently, Smith and coworkers published their economic analysis based on the French three-arm study of vinorelbine versus cisplatin and either vinorelbine or vindesine [85]. They found that the clinical benefit of cisplatin and vinorelbine was achieved at an acceptable cost per year of life gained compared with other regimens tested and compared with the combination of cisplatin and etoposide which was evaluated separately. These results cannot be accepted without some reservation: the Canadian study did not include the cost of CT-induced toxicities and was based on medical practice in the mid 1980s which may not be applicable to the 1990s, while the Smith study did not include costs of terminal care. In addition, costs of treatment will vary depending on the health care system and reimbursement strategy [86]. However, these studies represent the best evidence available, and collectively they suggest, contrary to the expectations of health care economists and many clinicians, that the cost effectiveness of CT for advanced NSCLC is well within the limits considered acceptable for medical interventions [87, 88].

CONCLUSIONS

Lung cancer will remain a major health problem worldwide. There is little evidence that current prevention programmes will lead to major reduction in the incidence of lung cancer in the next few decades so treatment strategies should focus on early detection and innovative therapies. Investigations are currently underway to examine the role of CT in early stage disease to confirm the results suggested by the meta-analysis. The feasibility of multi-course combination CT with RT and a concomitant radiosensitizing agent may improve local and distant relapse and studies are ongoing in locally advanced disease.

The last few years have seen a doubling of the number of active agents for this classically chemoresistant tumour. Phase II trials of combination regimens are underway and preliminary data are promising. If optimistic response and survival results reported from phase II trials are confirmed in phase III trials, studies in the adjuvant setting should follow.

After years of clinical investigation and conflicting results, there is now a firm foundation on which to build, and it is clear that CT prolongs survival of patients with locally advanced and metastatic disease. The next step is to identify better regimens which effect more clinically meaningful survival benefits and to decrease therapy-related toxicities to ensure that the added quality of life translates into improved QOL.

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