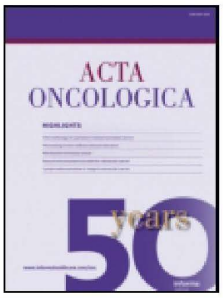

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A Systematic Overview of Chemotherapy Effects in Non-Small Cell Lung Cancer

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A systematic review of chemotherapy trials in several tumour types was performed by The Swedish Council of Technology Assessment in Health Care (SBU). The procedures for the evaluation of the scientific literature are described separately (Acta Oncol 2001; 40: 155–65). This overview of the literature on chemotherapy for non-small cell lung cancer (NSCLC) is based on 53 scientific publications including six meta-analyses based on 65 prospective randomised trials comprising 15 607 patients and an additional 32 prospective randomised studies including 8 902 patients. The conclusions reached can be summarised into the following points:

- In stage IIIB–IV disease, published data demonstrate that cisplatin-based chemotherapy confers a modest, median 1.5–3 months, prolongation of survival. The closely related compound carboplatin seems to provide similar effects. Randomised studies indicate symptomatic relief and improvement of indices of quality of life (QoL) for patients who receive platinum-based combination chemotherapy or single drug therapy with more recent compounds. Data supporting the use of chemotherapy are not available for patients in poor general condition (WHO performance status 3–4) and evidence is limited for elderly patients (above 70–75 years). Platinum-based chemotherapy can be recommended for selective use in routine care of advanced NSCLC although patients should be encouraged to participate in controlled clinical trials to further elucidate the role of chemotherapy in advanced disease.
- In advanced disease, recent data suggest that the newer agents gemcitabine, paclitaxel, irinotecan and vinorelbine, in combination with cisplatin, provide an additional survival benefit compared with earlier cisplatin-based regimens. Furthermore, paclitaxel, docetaxel and vinorelbine as single agents seemingly provide a survival benefit over supportive care alone comparable to that of older cisplatin-based combinations.
- A standard regimen for advanced disease cannot yet be defined. Until more data are at hand, it is recommended to be platinum-based and preferably combined with one of the newer agents.
- At progression after platinum-based chemotherapy for advanced disease, limited data indicate a small survival benefit from docetaxel over supportive care alone. Such second-line chemotherapy of advanced disease can be recommended for selected patients but should preferably be confined to controlled clinical trials.
- In stage III disease, published data show that induction cisplatin-based chemotherapy before radical radiotherapy modestly prolongs long-term survival and lowers the incidence of distant metastases compared with radiotherapy alone. Furthermore, published data show that concurrent chemo- and radiotherapy with cisplatin or carboplatin may enhance local control and long-term survival. Chemotherapy in this setting can be recommended for selected patients but treatment should preferably be given within a controlled clinical trial.
- In stage IIIAN2 disease, data from pilot studies demonstrate that surgery after induction chemotherapy is feasible. Pathologically complete remissions have been confirmed in 10–20% of treated patients. Two small randomised studies demonstrate a significant survival advantage for induction chemotherapy followed by surgery compared with surgery alone. Induction chemotherapy can be recommended for selected patients but treatment should preferably be given within a controlled clinical trial. The superiority of induction chemotherapy plus surgery compared with combined chemotherapy and radical irradiation has not been proven in a randomised trial but currently such studies are under way.
- In the adjuvant setting, published data suggest that cisplatin-based chemotherapy after radical surgery may increase five-year survival from around 50% by a further 5% but the confidence interval for this estimate is too wide for firm conclusions. Large-scale prospective randomised trials are under way to resolve this important issue and adjuvant chemotherapy is, thus, not recommended for routine treatment.

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In a global perspective, lung cancer is a major cause of cancer-related death. In Sweden, about 2 500 new cases of lung cancer are diagnosed clinically every year, with an additional 300 cases detected at autopsy. One-third of the patients are women and the incidence in females is steadily rising. In males, overall incidence has levelled off since about 1975. A more detailed analysis shows a statistically significant decline among men in larger Swedish cities, but not in the country as a whole (1). 80–90% of all lung cancer is caused by smoking alone or in combination with other factors.

The major histologic types of lung cancer according to the WHO classification, which was revised in 1999, are squamous cell carcinoma, small cell carcinoma, adenocarcinoma, large cell carcinoma, and adeno-squamous carcinoma. While small cell carcinoma exhibits specific characteristics with respect to clinical features and treatment principles, the other histologic types are frequently grouped together as non-small cell lung cancer (NSCLC) for practical purposes. In contrast to SCLC, which shows indisputable short-term sensitivity to antineoplastic drugs, NSCLC displays low or moderate sensitivity to chemotherapy and the clinical relevance of such treatment has been questioned. Since NSCLC accounts for about 80% of all lung cancer, acceptance of a role for chemotherapy in this tumour type would have considerable impact on the economy and organisation of care for lung cancer patients.

Staging of lung cancer is performed by use of the TNM system (Table 1). A modification of stage grouping according to TNM, based on data from a heterogeneous set of 5 319 patients diagnosed and/or treated at the University of Texas M. D. Anderson Cancer Center between 1975 and 1988, was published in 1997 (2). In the absence of impaired lung function or other medical contraindications to surgical therapy, patients with stages I and II disease are usually offered radical resection. Stage IIIA is a heterogeneous subset where some patients may be suitable for surgery. In stage IIIB, tumour growth is localised but too advanced for resection. In stage IV, distant metastases are confirmed. Non-surgical treatment, which may be considered in patients with early stage disease who cannot be operated for medical reasons and in patients with stage III–IV disease, offers at best very limited prospects for long-term survival.

Without treatment, the prognosis of NSCLC is poor. Based on follow-up of 130 patients who did not receive any specific anticancer therapy, median survival in stage IB was 17 months and all patients in this group were dead within three years from diagnosis. Patients with more advanced tumour stage (stages II–IV) had a median survival of eight months and all were deceased at 2.5 years (3).

After a basic evaluation, about 20% of lung cancer patients can be considered for surgery. In this group, five-year survival is in the order of 40–50% (4, 5). The vast majority of deaths during the first few years are due to lung cancer. In non-resected patients, five-year survival amounts to about 1%. The resection rate is, however, lower in some countries, and in the EUROCARE study, which reported 167 068 cases of lung cancer from 30 cancer registries in 11 countries between 1978 and 1985, relative five-year survival varied between 6 and 14% (6). These differences are too large to be explained solely by non-uniform methods of registration and implicate suboptimal standards for lung cancer detection and care in some parts of Europe. However, in all countries more than 50% of patients present with late stage disease (stage III/IV).

The role of chemotherapy in NSCLC has been the subject of considerable debate. This issue, as well as a number of other topics related to treatment of unresectable NSCLC, was reviewed in clinical practice guidelines forwarded by the American Society of Clinical Oncology in May, 1997. The conclusions were derived from an extensive review of published literature through April 1997, performed by a multidisciplinary panel (7).

It should be noted that response rate, which is a commonly used endpoint in studies of cancer chemotherapy, should be interpreted with caution in NSCLC. One major reason is the lack of consistent relationships between response rate and survival in randomised trials. In a study by the Eastern Cooperative Oncology Group (ECOG), 743 patients with stage IV NSCLC were randomised to receive one of five different regimens (8). When results for patients on a given regimen were compared with survival for all other patients, after adjustment for prognostic factors, carboplatin as a single drug was associated with the most favourable survival (median survival time, 32 weeks; $p = 0.008$). Response rate with carboplatin was, however, only 9%. In contrast, the combination of mitomycin, vinblastine, and cisplatin (MVP) showed a higher response rate of 20% but a trend for shorter survival (median survival time, 23 weeks; $p = 0.09$). Other examples of poor correlation between response rate and survival time in NSCLC may be found below.

A second limitation of response rate as a tool for evaluation of chemotherapy in NSCLC is observer variation. Application of WHO criteria for definition of response may be difficult in the presence of poorly defined boundaries of tumour and secondary inflammatory changes. Thirdly, it has been documented in studies of induction chemotherapy before surgery that the antineoplastic effect may be underrated by chest roentgenograms or CT examinations. Persistent radiographic changes do not exclude a pathological complete response. A reasonable explanation is that NSCLC tumours are composed of neoplastic cells as well as variable amounts of stromal tissue and the stromal component will not be affected by

Table 1

International TNM staging of lung cancer

TNM descriptors	
Primary tumour (T)	
TX	Primary tumour cannot be assessed, or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
T0	No evidence of primary tumour.
Tis	Carcinoma in situ.
T1	Tumour <3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus[1] (i.e., not in the main bronchus).
T2	Tumour with any of the following features of size or extent: >3 cm in greatest dimension; involves main bronchus, >2 cm distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung.
T3	Tumour of any size that directly invades any of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus <2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumour with a malignant pleural or pericardial effusion[2], or with satellite tumour nodule(s) within the ipsilateral primary-tumour lobe of the lung.
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of the primary tumour.
N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes(s).
N3	Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).
Distant metastasis (M)	
MX	Presence of distant metastasis cannot be assessed.
M0	No distant metastasis.
M1	Distant metastasis present.[3]

Stage grouping — TNM subsets	
Stage	TNM subset[4]
0	Carcinoma in situ
IA	T1N0M0
IB	T2N0M0
IIA	T1N1M0
IIB	T2N1M0
	T3N0M0
IIIA	T3N1M0
	T1N2M0
	T2N2M0
	T3N2M0
IIIB	T4N0M0
	T4N1M0
	T4N2M0
	T1N3M0
	T2N3M0
	T3N3M0
	T4N3M0
IV	Any T Any N M1

[1]The uncommon superficial tumour of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

[2]Most pleural effusions associated with lung cancer are due to tumour. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid show no tumour. In these cases, the fluid is non-bloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumour, the effusion should be excluded as a staging element and the patient's disease should be staged T1, T2, or T3. Pericardial effusion is classified according to the same rules.

[3]Separate metastatic tumour nodule(s) in the ipsilateral nonprimary-tumour lobe(s) of the lung also are classified M1.

[4]Staging is not relevant for occult carcinoma, designated TXN0M0.

non-surgical treatment. If irradiation is a treatment modality, postradiation fibrosis may further add to the difficulty of response evaluation by usual imaging methods.

In this review, the role of chemotherapy in NSCLC will be evaluated in four different contexts: (1) advanced disease (stage IIIB–IV), not amenable to surgical treatment or radical radiotherapy, (2) locally advanced disease (stage IIIA–B) in combination with radiotherapy, (3) as induction therapy before surgery (neoadjuvant therapy, in particular for stage IIIAN2), and (4) after radical surgery (stage I, II and subsets of stage IIIA).

The basis for the evaluation will be prospective randomised trials and meta-analyses of such studies. With few exceptions, only studies fully published in peer-reviewed journals will be taken into account. Endpoints will be QoL and duration of survival in advanced disease and long-term survival in settings 2–4 above.

ADVANCED DISEASE (STAGE IIIB–IV)

Role of cisplatin

A major international collaborative meta-analysis of the role of chemotherapy in NSCLC was published in 1995 (5). Individual updated information on 9 387 patients in 52 randomised trials was retrieved and the effect of chemotherapy on survival was reported in four different settings: chemotherapy vs supportive care in advanced disease, chemotherapy + radiotherapy vs radiotherapy alone for locally advanced disease, radical surgery followed by chemotherapy vs surgery alone, and surgery + postoperative irradiation followed by chemotherapy vs surgery + postoperative irradiation alone. The role of chemotherapy as related to surgery + postoperative irradiation will not receive major attention in this review. The principal reason is that postoperative radiotherapy has undergone critical re-evaluation in a recent meta-analysis (9).

In advanced disease, data were available from 11 trials (1 190 patients and 1 144 deaths). Eight trials used cisplatin-based chemotherapy and seven of these studies employed a combination of cisplatin with vinca alkaloids or etoposide. The results of trials using long-term alkylating agents suggested a detrimental effect of chemotherapy. However, cisplatin-based treatment compared with supportive care alone reduced the risk of death by 27% ($p < 0.0001$) and survival at one year was improved by 10% (95% confidence interval, CI: 5 to 15%) from 15% to 25%. Median survival increased from 4 to 5.5 (95% CI: 5 to 6.5) months. There was no evidence that any group of patients as defined by age, sex, histological type, performance status, or stage, had more benefit from chemotherapy.

In another analysis of comparative randomised trials confined to patients with advanced disease, survival at six months was chosen as endpoint. Individual patient data were not analysed. There were eight trials comprising a total of 712 patients and all studies but one used cisplatin-based chemotherapy in the comparison with best supportive care (BSC). The criteria for selection of trials were slightly different from those used in the study cited above. Seven of the trials were included in both analyses. The estimated pooled odds ratio of death was 0.44 (95% CI, 0.32–0.59) for patients receiving chemotherapy compared with patients treated by BSC alone, corresponding to an increase of median survival from 3.9 to 6.7 months (10).

A third analysis of randomised studies was performed by Souquet and others (11). Seven randomised studies comprising a total of 706 patients were examined with respect to mortality at 3, 6, 9, 12 and 18 months. Individual patients were not taken into account. Studies on single-drug treatment were excluded. Cisplatin was a component of chemotherapy in six trials. The seven studies form a subset of the 11 trials in the first meta-analysis. Mortality was significantly reduced during the first six months (three months; $p < 0.001$; six months; $p < 0.00001$) in patients receiving chemotherapy compared with BSC. The relative risk of death for patients who received combined chemotherapy was 0.65 at three months, 0.73 at six months, 0.86 at nine months, 0.91 at 12 months, and 0.96 at 18 months.

It is apparent from these studies that cisplatin-based chemotherapy confers a modest prolongation of survival in advanced NSCLC. The set of regimens is heterogeneous, as are entry criteria for various studies, and the optimal effect of chemotherapy on survival is probably underestimated. In addition, individual variability in response to treatment implies that gain of life may be more substantial in a proportion of cases. Questions related to optimal choice of drugs, doses, duration of chemotherapy as well as QoL and cost/benefit relationships are left unanswered by the meta-analyses.

The role of single-agent vs combination chemotherapy in advanced NSCLC was evaluated in an analysis by Marino and others (12). Nine studies comprising a total of 2 199 patients were reviewed and individual patient data were not taken into account. One-year survival was chosen as endpoint. The estimated pooled odds ratio of death for combination chemotherapy was 0.8 (95% confidence interval, 0.6–1.0). It should be noted that the only two trials showing a significant difference in favour of combined therapy compared single agent vinca alkaloid therapy with vinca akaloid + cisplatin (13, 14). Since the role of cisplatin has already been demonstrated in the meta-analysis by the Non-small Cell Lung Cancer Collaborative Group, it is doubtful if the study by Marino provides further information. With the advent of new active agents, further analyses of monotherapy vs combination chemotherapy in older trials are of limited interest.

Role of carboplatin

Cisplatin has been used in the vast majority of platinum-based treatment regimens. Comparable results may, however, be obtained with the analogue carboplatin (15),

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