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Current chemotherapy of advanced non-small cell lung cancer

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Systemic chemotherapy for patients with a good performance status and advanced non-small cell lung cancer may result in prolonged survival and improved quality of life. However, few single agents have an activity of more than 15% and they have significant toxicity. Cisplatin is widely regarded as the single agent of choice. Compared with single-agent therapy, two-drug combinations generally provide higher response rates although survival benefit is marginal. Three-drug combinations generally provide no additional efficacy benefit and are associated with greater toxicity. A cisplatin-based combination with one other agent provides the best currently available therapeutic index. Chemotherapy may also improve the patient's quality of life. The toxicity of current chemotherapy is an important factor and there is a clear need for new cytotoxic agents with equivalent or greater activity yet a more acceptable toxicity profile.

Introduction

Lung cancer is the most common cancer worldwide and results in approximately 1,000,000 deaths annually.[1] The pattern of disease seen at Groote Schuur Hospital is representative of that seen at major individual cancer treatment centres. In 1993, 378 newly diagnosed patients with lung cancer were seen. The histology was non-small cell lung cancer (NSCLC) in 82%. Many of the patients were relatively young at presentation; the median age of the patients was 59 years (range 31–89 years) and 25% of patients were under the age of 50 years. The majority were still in relatively good general condition and 68% of the patients had World Health Organization (WHO) performance status 0, 1 or 2 at presentation. However, only 15% of patients presented with stage I or II disease which is potentially curable by surgery, the remainder presenting with advanced disease. In this latter group the balance between efficiency and toxicity assumes special importance.

There has been recent interest in treating selected patients with advanced disease with chemotherapy to improve their survival or enhance their quality of life. This review cannot be fully comprehensive in view of the burgeoning literature but studies will be highlighted to present a perspective on the role of chemotherapy.

Active traditional agents

Few of the standard cytotoxic agents have shown response rates of more than 15% in pooled studies of over 100 patients with NSCLC.[2] Cisplatin, vindesine, mitomycin C and ifosfamide have shown response rates of 21%, 18%, 20% and 26%, respectively. Etoposide (response rate 9%) is often included amongst the active agents as it appears to be synergistic with cisplatin.[2] High-dose epirubicin has recently been reported to have a response rate of 19%.[3] The activity of agents determined from phase II studies cannot be compared with each other because of factors such as patient selection and quality control of response assessment. However, cisplatin has been regarded as the principal agent for NSCLC,[4] partly because of data from combination studies (see below). It is used nowadays with the 5-HT_3 antagonists to control nausea and vomiting which improves hydration and reduces its toxicity.

The combination of cisplatin and another cytotoxic agent is preferable to the use of non-cisplatin single-agent therapy; for example, a statistically significant increase in both response rate and survival has been found with cisplatin plus etoposide when compared with etoposide as a single agent (Table 1).[5] Combination chemotherapy is only marginally better, if at all, when cisplatin is the single agent. For example, a small gain in both response and survival, which was not statistically significant,

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Table 1. One vs two cytotoxics: cisplatin and etoposide was statistically significantly better than etoposide alone but not cisplatin alone

Study	Patients	Drugs	Response	Survival (wks)
Rosso[5]	193	Etoposide	7%	26
		PE	24%	35
Klastersky[6]	162	Cisplatin	19%	22
		PE	26%	26

PE = Cisplatin and etoposide.

was found with the combination of etoposide and cisplatin compared to cisplatin alone.[6]

The combination of three cytotoxics seems to result in the principle of diminishing returns and they do not appear to have an advantage over the use of two cytotoxics (Table 2).[7–9] In the three studies reported, response rate and survival with the three-drug combinations are either lower or equivalent to those obtained with two-drug combinations. The use of three drugs may, however, be expected to be associated with increased toxicity. An additional three-drug combination of mitomycin, ifosfamide and cisplatin[10] (MIC) results in a high response rate of over 50%, but the median survival is 9.2 months which may be similar to other regimens.

Chemotherapy and survival

The landmark report of the NCI of Canada in 1988 showed that chemotherapy caused a significant increase in survival in patients (Table 3).[7] Although the overall increase in survival with chemotherapy is only a few months (from 4 to 6–8 months), the median survival in responders is more prolonged, of the order of 12 months. Treatment was associated with significant toxicity, including grade 3–4 leukopenia in 38%–40% and neurotoxicity in 16% of patients receiving vindesine. It was recommended that treatment be offered to selected patients with review of the response and toxicity during chemotherapy.

Other studies of cisplatin-based chemotherapy compared to best supportive care (BSC) have tended to show favourable survival in the patients on chemotherapy (Table 3),[11–16] although only two of these trials were statistically significant.[15,16] A meta-analysis, however, has shown a modest overall increase in survival in patients with chemotherapy.[17]

Table 2. Two vs three cytotoxics: no improvement in response or survival was noted with the use of the three-drug combinations

Study	Patients	Drugs	Response	Survival (wks)
Rapp[7]	198	VP	25%	34.4
		CAP	15%	23
Crino[8]	136	PE	30%	37
		MEP	26%	35
Weick[9]	411	PE	16%	26
		VP	24%	23
		MVP	17%	22

CAP = Cyclophosphamide, doxorubicin and cisplatin; MEP = mitomycin, etoposide and cisplatin; MVP = mitomycin, vinblastine and cisplatin; PE = cisplatin and etoposide; VP = vindesine and cisplatin.

Table 3. Cisplatin-based combination chemotherapy vs best supportive care (BSC): there is an improvement in survival with chemotherapy

Study	Patients	Drugs	Survival (wks)
Rapp[7]	137	BSC	17
		CAP	24.7
		VP	32.6
Ganz[11]	48	BSC	13.6
		VP	20.4
Woods[12]	188	BSC	17
		VP	27
Kaasa[13]	87	BSC	16.5
		VP	22
Cellerino[14]	128	BSC	21.1
		CEP/MEC	34.3
Quoix *[15]	46	BSC	10
		VP	28
Cartei *[16]	102	BSC	16
		CCM	34

* Statistically significant. CEP = Cyclophosphamide, epirubicin and cisplatin; CAP = cyclophosphamide, doxorubicin and cisplatin; CCM = cisplatin, cyclophosphamide and mitomycin; MEC = methotrexate, etoposide and lomustine; MVP = mitomycin, vinblastine and cisplatin; VP = vindesine and cisplatin.

An independent analysis of the Canadian NCI study also showed that treatment was cost effective.[18] This is because patients on BSC required more in-patient stay than patients on chemotherapy. The use of out-patient (CAP) chemotherapy resulted in a net saving per patient (from Canadian $8,595 to $7,645). In-patient chemotherapy (VP) was associated with a total cost per patient of $12,230, but this was cost effective per year of life gained when compared with other standard med-

Table 4. Sample studies of new agents

Drug	Patients	Response	WHO grade 3 or 4 leukopenia	Other toxicity	Survival (wks)	Ref.
Gemcitabine	70	20% †	1%	Flu-like symptoms	37	24
Edatrexate	45	13%	8%	Mucositis	N/A	25
Irinotecan (CPT-11)	72	32%	25%	Diarrhoea	42	26
Vinorelbine *	206	14%	52%	Neurotoxicity	32	27
Paclitaxel	24	24%	75%	Hypersensitivity	40	28
Docetaxel	41	33%	97%	Fluid retention	47	29

* Data from phase III study. † Responses independently validated by external Oncology Review Board. N/A = Not available.

ical treatments. This study was undertaken prior to the availability of 5-HT_3 antagonists which allow chemotherapy to be given on an out-patient basis.

Chemotherapy and quality of life

There are relatively few data on the effect of chemotherapy on quality of life, perhaps because the latter is dominated by biological factors. The available data suggest that the improvement in patient's performance status and symptoms is higher than the objective response rate. In the report of 66 patients treated with the MIC regimen performance status improved, with an increase in the proportion of patients improving to performance status 0 and 1, from 45% prior to chemotherapy to 78% after chemotherapy in responding patients, and from 46% to 53% in non-responding patients.[19] In further reports of 45 patients treated with ifosfamide and cyclophosphamide,[20] and 24 patients treated with mitomycin, vinblastine and cisplatin,[21] an improvement in performance status was noted in 40% and 67%, a deterioration in 33% and 21%, and no change in 27% and 12%, respectively.

An improvement in symptoms in approximately 70% of patients has been documented with cisplatin-based combination chemotherapy. In two studies of 97 and 31 patients, pain improved in 77% and 47%, cough in 70% and 45%, haemoptysis in 92% and 91%, dyspnoea in 46% and 78%, and malaise in 58% and 50% of patients, respectively.[19,22] Symptom improvement was higher in patients responding to chemotherapy. In the latter study,[22] quality of life was also assessed, using a visual analogue scale, and an improvement was found in 75% of patients. These data are encouraging but need to be confirmed in larger studies and symptom improvement counterbalanced with the toxicity of treatment.

New agents

Decreased drug toxicity and patient convenience (for example, out-patient drug administration) are particularly important to improve quality of life in patients with NSCLC in view of the onerous nature of the disease. Active agents which have a novel method of action are also potentially useful in combination therapy. A number of new drugs have shown activity in phase II studies of NSCLC and these have been recently reviewed.[23] The response rates and toxicity of sample studies of these agents are described in Table 4.[24–29] Among the most promising agents are gemcitabine and edatrexate which are anti-metabolites, irinotecan (CPT-11) which is a camptothecin and a topoisomerase 1 inhibitor, and vinorelbine, paclitaxel and docetaxel which act on the cell spindle. The possible role of these drugs in single-agent and in combination therapy is being vigorously investigated.

Conclusions

There has been progress in the chemotherapy of NSCLC over the last 5 years and chemotherapy regimens have been better defined. Published randomized trials would indicate that a two-drug combination including cisplatin is close to the optimal available therapy. Chemotherapy can prolong patient survival, with the major benefit being seen in responding patients. Chemotherapy may also improve patients' quality of life, although the data are limited. The toxicity of current chemotherapy is, however, considerable, and its use requires a continual cost–benefit assessment by patients and physicians. New agents which may be useful in the management of advanced NSCLC have been identified and are currently being evaluated in single-agent and combination regimens.

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