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Improving Quality of Life in Patients with Non-small Cell Lung Cancer: Research Experience with Gemcitabine

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Alongside objective response rate, quality of life of patients is important in the treatment of cancer, particularly in the palliative setting. Quality of life is difficult to define precisely and is correspondingly difficult to assess. However, a number of methods have been devised and self-report questionnaires are now widely used. Patients with metastatic non-small cell lunger cancer (NSCLC) have a poor prognosis with few patients surviving longer than 8 or 9 months. Curative treatment is often not possible and few patients receive active treatment. Although some patients will accept toxic treatments in return for increased survival, it is generally hoped that any treatment, curative or palliative, will not adversely affect patients' quality of life. In three studies in which gemcitabine was used as a single agent in metastatic NSCLC, objective response rates of 20% were obtained. Gemcitabine was well tolerated. Symptoms improved in the studies where disease-related symptoms were assessed. The degree of improvement compared well with historical data on the relief offered by standard radiotherapy and combination chemotherapy. These findings have led to the initiation of a randomised trial to compare the relief offered by gemcitabine plus best supportive care with best supportive care, using quality of life assessments as a primary endpoint. © **1997 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

THE GOAL of treating cancer is to cure the patient, but in many cases this is not possible and the objective becomes prolongation of life and maintenance of its quality. However, 'quality of life' is a general concept and has proved difficult to define precisely. It describes a sense of well-being and includes several factors such as physical symptoms and function, psychological well-being, social interaction (family and professional life) as well as economic aspects [1]. The individual importance of each factor may vary, with any particular factors(s) being predominant at any point in time. In addition, individuals put differing values on these factors according to changing priorities and health status and this must be taken into account when assessing quality of life. A good quality of life is not necessarily 'normality' for that patient, nor an ideal of perfect quality of life, but the perspective of the patient, not the health professional, must be paramount.

Concern for maintaining quality of life for patients has always been an important issue in oncology and its precise measurement is becoming more and more important and in some cases mandatory. Both the disease, and in many cases its treatment, have profound physical and emotional effects on patients. Patients must come to terms with a distressing, possibly terminal, condition and may feel there is a stigma attached to it. The net benefit of treatment must be assessed (i.e. treatment may increase survival but may be associated with side-effects). Measuring the quality of life in cancer patients allows us to assess support needs, evaluate treatment outcomes and predict effects of future treatment [2]. In the longer term, policy decisions may be made after studying the effects of different management options on the quality of life of patients.

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Measuring quality of life in patients with cancer

The aim of quality of life assessments in cancer clinical trials is to provide systematic data about patients' disease symptoms, treatment side-effects and their significance. This complements the traditional outcome measurements of tumour response, toxicity and survival time.

In order to assess the many and varied effects of disease and treatment, the concept of 'quality of life' has to be broken down into measurable variables. A number of methods of measurement have been devised incorporating the various dimensions used in the definition of quality of life (physical, psychological, functional and social). The choice of method will depend on the type of clinical trial and on the precise research question being addressed.

Some quality of life measures are completed by observers, for

example, health professionals treating the patient. Loss of hair and physical function may be evaluated in this way, but this gives no impression of how the patient is coping with treatment. Patients need to assess themselves on factors such as emotional effects because of their subjective nature. The ideal is to measure the patients' experience together with the situation as observed by others (e.g. physician or other carers). Semi-structured or unstructured interviews can provide detailed information and allow the patient a high degree of self-expression, but are time-consuming and impractical in the clinical trial setting. Patient diaries are helpful when frequent recording of symptoms is important. However, the most usual method of assessing quality of life in cancer trials is the multidimensional self-report questionnaire. This is widely applicable for cancer trials, especially those with large numbers of patients, although, in the palliative treatment setting, compliance may be a problem. Several formats of questionnaires have been designed so that responses may be a simple 'yes' or 'no' or a limited range of responses may be defined (e.g. not at all/a little/quite a lot/very much). Visual analogue scales give scope for a range of replies and can also cover a wide variety of domains. All methods have their strengths and weaknesses and should be selected according to the needs of a particular trial. Only those questionnaires that assess several dimensions are designated 'quality of life' measures, so that performance indices and psychological scales are insufficient unless used in combination with other questionnaires.

The most widely used quality of life questionnaires consist of general 'core' questions accompanied by a specific subscale for disease- or treatment-related symptoms associated with a particular tumour type. The questionnaire devised by the QOL Study Group of the European Organisation for the Research and Treatment of Cancer (EORTC) is based on this approach and is increasingly used in clinical trials of new anticancer drugs. This self-administered questionnaire is referred to as QLQ-C30 [3]. It has 30 questions incorporating five functional scales (physical, role, cognitive, emotional and social), a global quality of life scale, three symptom scales (fatigue, pain and nausea and vomiting), and a number of single-item measures. The acceptability, reliability and validity of the questionnaire has been confirmed in patients with lung cancer. Most of the functional and symptom measures were able to discriminate between patients differing in clinical status as defined by ECOG performance status, weight loss and treatment toxicity, and the questionnaire showed responsiveness to changes in health status over time. In addition, the group developed a complementary questionnaire to address disease symptoms and treatment side-effects relevant to lung cancer patients that were insufficiently covered by the core questionnaire [4]. This lung cancer module, LC13, consists of two multi-item scales (dyspnoea and pain) and six single items referring to physical symptoms and side-effects. Data are available from 883 lung cancer patients to support the psychometric properties of the instrument. Although further refinement to this scale is proposed, it currently represents one of the most promising tools for assessing disease symptoms in lung cancer patients.

A number of other quality of life scales of equal merit have been published in recent years and are also widely used. These include the Rotterdam Symptom Checklist [5], the Functional Assessment of Cancer Therapy [6] and the Functional Living Index—Cancer [7]. The selection of the most appropriate scale is clearly a fundamental part of quality of life protocol design, but many other theoretical and practical issues need to be addressed if good quality data are to be achieved. Quality of life endpoints have already been incorporated in clinical trials for non-small cell lung cancer (NSCLC) and aspects of design, implementation and analysis have proved to be somewhat more problematic than anticipated [8].

Role of best supportive care and chemotherapy in maintaining/improving the quality of life of patients with NSCLC

The prognosis for patients with metastatic NSCLC is poor with the median survival duration not exceeding 8–9 months in large prospective studies. Although, at present, surgery or radical radiotherapy in highly selected patients offer the only prospect of cure, many patients have locally advanced or metastatic disease at diagnosis and would not benefit from these local treatments. Such patients have a considerable burden of symptoms at presentation [9] and chemotherapy seems to represent the best chance for an improved outcome. However, its role is controversial, and there is no standard treatment. Many cytotoxic drugs have been used in NSCLC, but only a few have been reported to have reproducible response rates $> 15\%$ including ifosfamide, vindesine, vinblastine, cisplatin and mitomycin [10]. Administering these drugs in combination may increase response rates, but the data are equivocal and details of symptom palliation and impact on quality of life are often lacking. Trials aimed at demonstrating an improvement in survival have also yielded equivocal data. There is a belief amongst clinicians that a patient's performance status and quality of life are likely to deteriorate with chemotherapy, although patients themselves may be willing to trade considerable toxicity for small gains in symptom relief or survival [11]. Therefore, to assess whether chemotherapy has a role in the management of NSCLC, studies comparing chemotherapy with best supportive care are essential. Best supportive care is often poorly defined and quantified, but is usually described as any palliative therapeutic modality that may be offered to a patient with NSCLC excluding chemotherapy but including radiotherapy and non-cytotoxic medication.

Some early studies reported that chemotherapy offered no survival advantage over best supportive care and in some cases resulted in worse survival (Table 1). However, these studies used drugs that are now considered ineffective. Later studies show that chemotherapy offers a modest survival advantage (Table 2). In a recent meta-analysis of 11 trials and 1190 patients, there was a 10% improvement in the 1-year survival rate (from 16% to 26%) and a 2-month improvement in median survival (from 6 months to 8 months) for platinum-based regimens compared with best supportive care [12] indicating that NSCLC patients can benefit from chemotherapy.

To date, few patient-generated data have been published to quantify the benefit of chemotherapy in terms of specific quality of life parameters. The reasons for this are varied. Firstly, it is only in the recent past that well-constructed quality of life questionnaires have become available. Adequate measurement of quality of life should no longer be a limiting factor, and there is a good deal of clinical research underway. More persistent limitations include the problems of implementing quality of life protocols successfully in the palliative setting, such as high patient attrition rates, limited compliance and the need for infrastructure and resources to administer forms to patients. More sophisticated statistical methods of analysis are also needed to produce outcomes that will be easily understood and used by clinicians.

Previously doctors have lacked a commitment to quality of

Table 1. Chemotherapy versus best supportive care in locally advanced and metastatic NSCLC: older trials

Reference	No. patients (all groups*)	Regimen	OR (%)	Median survival (months) CT versus no CT		% survival at 1 year CT versus no CT	*P* value
Wolf and associates (1960) [20]	168	N_2M	NR	4.3	3.3	NR	NR
Green and associates (1969) [21]	1364	N_2M	NR	2.6	2.2	NR	NS
		Cyclo	NR	2.9			
Durrant and associates (1971) [22]	249	N_2M	NR	8.7†	8.4†	NR	NS
Laing and associates (1975) [23]	188	PCZ	NR	6.9	7.9	NR	<0.05
		MVPP	NR	2.7			

* Total number of treated and control patients. † mean survival. OR, objective response; CT, chemotherapy; N_2M, nitrogen mustard; cyclo, cyclophosphamide; PCZ, procarbazine; MVPP, nitrogen mustard, vinblastine, procarbazine, prednisolone; NR, not recorded; NS, not significant, $P > 0.05$.

Table 2. Chemotherapy versus supporting care in locally advanced and metastatic NSCLC: recent trials

Reference	No. patients (all groups*)	Regimen	OR (%)	Median survival (months) CT versus no CT		% survival at 1 year CT versus no CT		*P* value
Cormier and associates (1982) [24]	39	MACC	35	7.6	2.1	35	6	0.005
Rapp and associates (1988) [25]	150	CAP	15	6.1	4.2	21	10	0.01
		PV	25	8.1		22		
Ganz and associates (1989) [26]	48	PVb	22	5.1	3.3	20	10	NS
Woods and associates (1990) [27]	201	PV	28	6.8	4.3	NR	NR	NS
Buccheri and associates (1990) [28]	175	MACC	8	8	5	27	17	0.01
Kaasa and associates (1991) [29]	87	PE	11	5.0	3.8	NR	NR	NS
Cellerino and associates (1991) [30]	128	CEP/MEC	21	8.5	5	32	23	NS
Quoix and associates (1991) [31]	49	PV	42	7.1	2.6	NR	NR	< 0.001
Leung and associates (1992) [32]	119	PE	21	12.4	8.7	53	30	0.05
Cartei and associates (1993) [33]	102	PCM	25	8.5	4.0	39	12	0.0001

* Total number of treated and control patients. OR, objective response; CT, chemotherapy; MACC, methotrexate, doxorubicin, cyclophosphamide, CCNU; CAP, cyclophosphamide, doxorubicin, cisplatin; PV, cisplatin, vindesine; PVb, cisplatin, vinblastine; PE, cisplatin, etoposide; CEP, cyclophosphamide, epirubicin, cisplatin *alternating* with MEC (methotrexate, etoposide, CCNU); PCM, cisplatin, cyclophosphamide, mitomycin C; NR, not recorded; NS, not significant, $P > 0.05$.

life research, perhaps because of doubt about its clinical utility, but there has been a considerable change in attitude in the 1990s so that quality of life protocols are now mandatory in many studies.

Experience with gemcitabine

Gemcitabine is a new cytotoxic agent which is active and also well tolerated, thus distinguishing it from many existing drugs. Three studies of single-agent gemcitabine in advanced NSCLC have been completed [13–15] (Table 3). All used a starting dose of 800–1250 mg/m^2 every 3 weeks followed by a week of rest. Response rates of 20% were recorded and validated by an independent oncology review board. In an early American study the response rate was only 3%. However, the dose delivered in this study was significantly lower (the mean dose was < 700 mg/m^2) than in the other studies. In addition, patients in this study were older and had a higher incidence of previous radiotherapy to the primary thoracic tumour. In the extended study, the response rate increased to 26% [16].

In all of these studies, gemcitabine was well tolerated as judged by clinicians [17] and myelosuppression was mild. Anaemia was not a significant problem with WHO grade 3 and 4 anaemia occurring in < 7.2% and 6.1% of patients, respectively. It was managed with the use of conventional transfusions. Neutropenia grade 3 and 4 occurred in < 26% and 6% of patients, respectively, and the incidence of infection associated with this level of neutropenia was low; grades 1 and 2 infection toxicity were reported for 7.9% and 1.7% of patients, respectively. No grade 3 or 4 infection toxicity was reported. Thrombocytopenia grade 3 and 4 was rare. Modest hepatotoxicity was seen, manifest as transient, asymptomatic, rapidly reversible elevation of liver enzymes. Other toxicities that were not dose-limiting included skin rash, mild fever on the day of treatment, proteinuria and lethargy. Flu-like symptoms were reported in 23.3% of patients. The symptoms were usually mild, short-lasting (often on day of treatment only) and rarely dose-limiting. The mechanism of this event is unknown, but symptoms may be relieved by paracetamol. Peripheral oedema was also reported as a serious adverse event in 1.9% of patients, but this was not associated with any evidence of cardiac, hepatic or renal failure. Hair loss was infrequent. However, the subjective impact of such toxicities on patients' quality of life has not been systematically evaluated.

Disease-related symptoms were monitored in all patients in the European and international studies where gemcitabine was administered as a single agent. Symptom improvement had to be maintained for at least 4 weeks to be considered clinically relevant and patients were coded according to the worst symptom experienced between clinic visits irrespective of the duration of symptom. No symptomatic treatment (e.g. steroids) was allowed. Symptom improvement data, objective response and survival for gemcitabine were compared with published data for radiotherapy (MRC study) and combination chemotherapy [18, 19] (Table 4). The symptom relief offered

Table 3. Response rates in phase II trials of single-agent gemcitabine for NSCLC (American, European, South African and International studies)

	American*	S. African [13]	European [14]	International [15]
Number of patients enrolled/evaluable	34/30	84/76	82/71	161/151
Median age (range)	64 (40–78)	59 (36–75)	57 (23–71)	59 (35–75)
Gender (M/F)	29/5	65/19	49/33	124/37
Performance status (WHO)				
0	6 (17.6%)	2 (2.4%)	20 (24.4%)	17 (10.6%)
1	26 (76.5%)	81 (96.4%)	45 (54.9%)	134 (83.2%)
2	2 (5.9%)	1 (1.2%)	16 (19.5%)	10 (6.2%)
3	—	—	1 (1.2%)	—
Stage				
IIIa		15 (18%)	18 (22.0%)	7 (4.3%)
IIIb	34	34 (40.5%)	24 (29.3%)	50 (31.1%)
IV		35 (41.7%)	40 (48.8%)	104 (64.6%)
Histology				
Squamous	13 (38.2%)	39 (46.4%)	24 (29.3%)	70 (43.5%)
Adenocarcinoma	18 (52.9%)	21 (25.0%)	53 (64.6%)	84 (52.2%)
Mixed	–	3 (3.6%)	—	6 (3.7%)
Large cell	2 (5.9%)	10 (11.9%)	1 (1.2%)	Excluded
Undifferentiated	1 (2.9%)	8 (9.5%)	4 (4.9%)	1 (0.6%)
Small cell	—	1 (1.2%)	—	—
Others	—	2 (2.4%)	—	—
Previous radiotherapy	8 (23.5%)	8 (9.5%)	2 (2.4%)	Excluded
Response				
Complete response	0	2 (3%)	0	3 (2%)
Partial response	1 (3%)	13 (17%)	16 (22.5%)	30 (20%)
Overall response	3%	20%	22.5%	21.9%
95% confidence interval	1–17%	11.5–30.5%	13.5–34%	15.5–29.3%
Response duration (months)				
Median	16.9†	8.1	12.7	7.6
Range	N/A	3.6–17.3‡	4.6–14.8‡	2.6–10.6‡
Median survival (months)	8.8	8.1	9.2	8.9

* F.O. Butler, Methodist Hospital, Indianapolis, Indiana, U.S.A. † One patient. ‡ Data censored, patients are still responding and the upper limit may increase.

Table 4. Symptom improvement data, objective response and survival for gemcitabine alone, radiotherapy and combination chemotherapy

Symptom improvement	Gemcitabine studies*		Radiotherapy two fractions/multiple fractions (MRC) [19]	Combination chemotherapy MIP (Cullen) [18]
	All patients	Mod/sev		
Cough	44%	73%	65/56%	70%
Haemoptysis	63%	100%	81/86%	92%
Pain	32%	37%	75/80%	77%
Dyspnoea	26%	51%	66/57%	46%
Anorexia	29%	38%	68/64%	58%
Response	20%		30%	56%
Survival (months)	8.1–9.2		6.4	9.8

* No steroids. MRC, Medical Research Council; MIP, mitomycin C, ifosfamide, cisplatin; Mod/Sev, subgroup of patients with moderate–severe symptoms treated with gemcitabine.

by gemcitabine compared well with that from these two other treatment approaches. The patients' reporting of symptom relief was supported by the clinicians' assessments of performance status. In the European study, conducted jointly between Copenhagen and Manchester, 31% of patients improved (defined by at least four consecutive observations with scores better than baseline over a period of 7 days or longer). Performance status remained stable in a further 67% of patients, and deterioration was seen in only 2% of patients. When data from the European and international studies were combined, 52% of patients improved from performance status 2. It should be noted that the symptomatic response rate for gemcitabine was higher than the objective tumour response rate.

There are no published trials of chemotherapy versus best supportive care with quality of life as a primary endpoint, and this is clearly an area where further trials are needed. In view of the promising results with gemcitabine, a study has been designed to compare gemcitabine and best supportive care with best supportive care alone. Patients in both arms of the study receive full supportive care, including radiotherapy. However, chemotherapy other than gemcitabine is not permitted and radiotherapy in the gemcitabine arm defines treatment failure. The primary objective of the study is to compare changes from baseline in the patient-assessed disease-related symptoms and the quality of life experienced by chemonaive patients with locally advanced or metastatic NSCLC. The endpoints for this trial will be measured using the EORTC QLQ-C30 and LC13, the lung cancer specific module. Secondary objectives include quality of life response (a quality of life responder is empirically defined as any patient with an improvement of 25% or greater in total score from baseline to 2 months of the EORTC QLQ-C30 symptom scale maintained for at least 1 month), overall survival and physician-assessed disease-related symptom improvement.

CONCLUSIONS

Chemotherapy offers an advantage over palliative care alone in patients with NSCLC, because of its potential to increase survival and improve quality of life. The response rates reported in studies of single-agent gemcitabine in NSCLC compare well with those of standard cytotoxic drugs. Gemcitabine is well tolerated with few side-effects. In addition, gemcitabine has a palliative effect improving both disease-related symptoms and performance status, indicating that these aspects of quality of life in these patients are improved. The trial currently underway will allow a more detailed evaluation of these benefits and will provide a basis from which to plan and compare future treatment strategies.

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