Eur J Cancer, Vol. 27, No. 5, pp. 674–675, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00
Pergamon Press plc

A Phase II Study of Vindesine plus Etoposide in Metastatic Non-small Cell Lung Cancer

P.S.G.J. Hupperets, G.P.M. ten Velde, H. Bron, L. Schouten and G.H. Blijham

THE PROGNOSIS of patients with locally advanced non-small cell lung cancer (NSCLC) is dismal. With cisplatin-containing chemotherapy, response rates in locally advanced and metastatic disease in large multicentre trials are around 20–30% [1–4]. In randomised trials, cisplatin containing regimens did not show a significant prolongation of survival when compared to maximal supportive care in patients with metastatic or bulky limited NSCLC, but added considerable toxicity [5]. These data indicate that the beneficial effect of cisplatin-containing therapy in NSCLC remains questionable. Vindesine and etoposide are both active as single agents in NSCLC. Cytokinetically, etoposide acts by arresting cells in the premitotic stage, in particular the S and G2 phases. Vinca alkaloids arrest cells in metaphase. We have studied the efficacy and toxicity of a combination of these drugs in NSCLC.

Patients with metastatic NSCLC, Karnofsky index above 50%, no prior chemotherapy and a life expectancy of more than 12 weeks were eligible. Patients without adequate bone marrow reserve and aged over 70 years were not eligible. Pretreatment investigations included haemoglobin (Hb), white blood cells (WBC) and differentiation of leucocytes, platelets, creatinine, albumin, chest X-ray and computer scanning or echography of the metastatic tumour. Vindesine 3 mg/m^2 was given intravenously every week for 8 consecutive weeks. Etoposide was given as 200 mg/m^2 orally once a day for three consecutive days every 3 weeks with day 3 of etoposide being the day of vindesine administration. If at the time of evaluation a partial response (PR), complete response (CR) or stable disease (SD) was reached, vindesine and etoposide were offered in a three-weekly schedule. Responses were evaluated according to the WHO criteria. Treatment was postponed in case of myelosuppression to less than 2000/μl WBC and/or less than 75 000/μl platelets; in case of WBC between 2000 and 3000/μl and/or platelets between 75 000 and 100 000/μl both drugs were given at a 50% dose level. Evaluation of the response took place after 8 weeks of treatment.

28 patients with metastatic NSCLC entered the study. The mean Karnofsky index was 70 (range 50–90). All patients were pretreated by irradiation on the primary tumour and mediastinum. 16 NSCLC were squamous cell carcinoma, 10 adenocarcinoma and 2 large cell carcinoma. The mean age of all patients was 53 years (range: 30–71). The sites of metastatic disease are listed in Table 1. 8 patients did not complete the 8 weeks treatment period because of progressive disease. These patients are included for response evaluation and survival. The total response rate was 21% (6/28 patients); 1 patient had a complete response (Table 1). This patient had a metastatic mass localised in the supraclavicular region from a primary squamous cell carcinoma. 26% (8/28) of the patients had stable disease. The median duration of response in the 6 responding patients was 24 weeks whereas the median progression free period for all patients was 17 weeks. The median duration of survival calculated from the start of treatment in all patients was 165 days. Bone marrow toxicity was evaluated weekly during the first 8 weeks of the treatment. Six episodes of bone marrow toxicity of WHO grade 4 were scored without infectious complications. In Table 2, an overview is given of the different toxicities in WHO grading. In 1 patient the treatment had to be discontinued because of toxicodermia after administration of vindesine.

Table 1. Response by tumour site

Localisation	No. of patients	CR	PR
Supraclavicular mass	4	1	1
Lung only	6	–	1
Liver only	4	–	–
Mediastinum only	1	–	–
Lung plus liver or bone	3	–	2
Other	10	–	1

CR = complete response, PR = partial response.

Table 2. Toxicity

WHO grade	0	1	2	3	4
Neurotoxicity	18	5	3	2	0
Leucocytopenia	0	4	8	10	6
Anaemia	15	7	4	2	0
Thrombocytopenia	25	3	0	0	0
Alopecia	0	6	12	10	0

Maximum toxicity grade documented for each patient during treatment.

In this study a combination of vindesine and etoposide was found to have a response rate of 21% (95% confidence interval 5%–33%) in patients with metastatic NSCLC. This response rate is at the lower end of the results obtained with cisplatin containing regimens [1–7]. The overall survival obtained in this study does not appear to be different from that of studies using cisplatin containing regimens. The toxicity of this regimen is a major concern. About half the patients had a grade 3 or 4 bone marrow toxicity in particular leucocytopenia; however, serious infections and septic periods were not recorded. Subjective toxicity consisted mainly of grade 3 alopecia and some neurotoxicity. Taken together, this regimen does not appear to represent an improvement over cisplatin containing regimens. Also, in view of the appreciable toxicity it is not an attractive alternative for these regimens nor a starting point for the addition of other cytostatic agents.

Correspondence to P.S.G.J. Hupperets.
P.S.G.J. Hupperets and G.H. Blijham are at the Department of Internal Medicine, Division of Haematology-Oncology; G.P.M. ten Velde is at the Department of Pulmonology, Academic Hospital Maastricht, P.O. Box 1918, 6201 BX Maastricht; H. Bron is at the Department of Internal Medicine, Maasland Hospital Sittard; and L. Schouten is at the Registration Department, Comprehensive Cancer Center Limburg, Maastricht, the Netherlands.
Revised 6 Feb. 1991; accepted 8 Feb. 1991.

1. Cellerino R, Tummarello D, Porfiri D, *et al.* Non small lung cancer (NSCLC). A prospective randomized trial with alternating chemotherapy CEP/MEC versus no treatment. *Eur J Cancer Clin Oncol* 1988, **24**, 1839–1843.

2. Williams CJ, Woods R, Levi J, *et al.* Chemotherapy for non-small cell lung cancer: a randomized trial of cisplatin/vindesin vs no chemotherapy. *Semin Oncol* 1988, **15**(Suppl. 7), 58–61.
3. Einhorn LH, Loehrer PJ, Williams SD, *et al.* Random prospective study of vindesin versus vindesin plus high dose cisplatin versus vindesin plus cisplatin plus mitomycin-C in advanced non small cell lung cancer. *J Clin Oncol* 1986, **4**, 1037–1041.
4. Hainworth JD, Johnson DH, Hande KR, *et al.* Chemotherapy of advanced non small cell lung cancer: a randomized trial of three cisplatin-based chemotherapy regimens. *Am J Clin Oncol* 1989, **12**, 345–349.
5. Ruckdeschel JC, Finkelstein DM, Ettinger DS, *et al.* A randomized trial of the four most active regimens for metastatic non small cell lung cancer. *J Clin Oncol* 1986, **4**, 14–17.
6. Rapp E, Pater JL, Willian A, *et al.* Chemotherapy can prolong survival in patients with advanced non small cell lung cancer: report of a Canadian multicenter randomized trial. *J Clin Oncol* 1988, **6**, 633–641.
7. Hesketh PJ, Cooley TP, Finkel HE, *et al.* Treatment of advanced non small cell lung cancer with cisplatin, 5-fluorouracil and mitomycin-C. *Cancer* 1988, **62**, 1466–1470.

Eur J Cancer, Vol. 27, No. 5, p. 675, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00
Pergamon Press plc

Outcome Following Treatment for Head and Neck Cancer: Beyond Clinical Assessment

Jenny Morris

TWO RECENT reviews have indicated that the psychosocial sequelae of treatment associated with cancers of the head and neck region are relatively unexplored [1, 2]. Problems identified included speech and eating difficulties, social and marital problems, increased levels of anxiety and depression. However, there were several methodological problems associated with many of the studies which can be summarised as follows: (i) the majority were retrospective, based on small samples which in general were not stratified by stage of disease and did not include control groups; (ii) the measures of quality of life tended to be rather crude and largely focused on functional parameters: none of the studies used instruments utilised in studies of other cancer patients (eg. the Rotterdam Symptom Checklist, the Spitzer QL index, the Functional Living Index for Cancer, the EORTC quality of life questionnaire); (iii) none of the studies investigated the role of individual differences (eg. coping style, levels of self-esteem, social support) and how these might influence outcome.

As a consequence, the extent to which the psychosocial problems experienced by this group of patients can be attributed to treatment remains relatively unknown. Additional work needs to be undertaken using controlled trials to measure the quality of life in head and neck cancer patients. Instruments which have been shown to be both reliable and valid in studies with other cancer patients should be used to assess the impact of diagnosis and treatment on psychological, social, occupational and sexual functioning. Where possible, questionnaires should be completed by the patients themselves as this has been shown to be a more reliable method than relying on quality of life assessments made by doctors and nurses [3].

Quality of life data can provide important additional information to be used in the decision making process especially where two forms of treatment are known to be equivalent in terms of survival, or where the aims of treatment are palliative rather than curative. Decisions about treatment for head and neck cancers inevitably involve tradeoffs between length of survival and quality of life and there may well be differences between patients regarding the extent to which they would wish to trade quality of life for length of survival. If quality of life information is well documented for the post treatment period then this will help provide doctors and patients with more information to help maximise lifestyle and trade disability from treatment for potential survival.

Although cancers of the head and neck region are relatively uncommon, some of them are among the most preventable of tumours as they are most prevalent in individuals who have a history of heavy drinking and/or smoking [4]. Thus questions might be asked about the opportunity costs of providing relatively expensive treatment to patients with advanced disease compared to financing health education programmes, or ensuring general practitioners are alerted to the need to screen individuals at most risk of developing such cancers. Such issues are of particular relevance for patients with head and neck cancers because they often present with advanced disease and also because they may continue to smoke or drink heavily during/after treatment which increases the risk of recurrence.

Methods of economic evaluation which can be used in combination with quality of life assessment include cost-effectiveness analysis and cost-utility analysis [5, 6]. By combining information relating to quality of life and costs, comparisons of the relative costs of achieving different outcomes can be made.

In summary, the evaluation of the quality of life of patients following treatment for cancers of the head and neck region could provide useful information which would: (i) aid decision making where different modes of treatment result in similar clinical outcomes; (ii) provide a focus for rehabilitation programmes; (iii) help identify those individuals unlikely to cope with the consequences of diagnosis and treatment in order that they may receive additional support. Together with economic evaluations, such data would also provide more comprehensive information on the costs and consequences of alternative uses of health care resources than that currently provided by mortality statistics.

Correspondence to J. Morris, Centre for Health Economics, University of York, York YO1 5DD, U.K.
Revised 28 Jan. 1991; accepted 8 Feb. 1991.

1. Pruyn J, Jong P, Bosman L, *et al.* Psychosocial aspects of head and neck cancer — a review of the literature. *Clin Otolaryngol* 1986, **11**, 469–474.
2. Morris J. The quality of life of head and neck cancer patients: a review of the literature. Discussion Paper 72, Centre for Health Economics, York, 1990.
3. Slevin M, Plant H, Lynch D, Drinkwater J, Gregory W. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988, **57**, 109–112.
4. Boyle P, Macfarlane G, Maisonneuve P, Zheng T, Scully C, Tedesco B. Epidemiology of mouth cancer in 1989: a review. *J R Soc Med* 1990, **83**, 724–730.
5. Drummond M, Stoddart G, Torrance G. *Methods for Economic Evaluation of Health Care Programmes*. Oxford, Oxford University Press, 1987.
6. Feeny D, Labelle R, Torrance G. Integrating economic evaluations and quality of life assessments. In: Spilker B, ed. *Quality of Life Assessments in Clinical Trials*. New York, Raven, 1990, 71–83.