6. Camaggi CM, Strocchi E, Carisi P, Martoni A, Pannuti F. High-dose epirubicin in advanced cancer: a cross-over investigation of pharmacokinetic linearity. *Proc ASCO* 1990, **9**, 81.
7. Miller AB, Hoogstraten B, Staquet H. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
8. Pannuti F, Martoni A, Piana E, Palenzona D. Proposta di un modello di valutazione della tossicita in chemio-ormonoterapia antiblastica. *Min Med* 1978, **69**, 3761–3772.
9. Martoni A, Giovannini M, Tomasi L, *et al.* A phase II clinical trial of 4'-epidoxorubicin in advanced solid tumors. *Cancer Chemother Pharmacol* 1984, **12**, 179–182.
10. Feld R, Wierzbicki R, Walde D, *et al.* High dose epirubicin given as daily × 3 in patients with untreated extensive non-small lung cancer. A phase I-II study. *Proc AACR* 1988, **29**, 208.
11. Holdener EE, Jungi WJ, Fiebig H. Phase I of high dose epirubicin in NSCLC. *Proc ASCO* 1988, 7, 806.
12. Henss H, Fiebig HH, Holdener EE, Kaplan E. Phase II study of high-dose epirubicin in non-small cell lung cancer. *Contrib Oncol* 1989, **37**, 136–140.
13. Wils J, Utama I, Sala L, *et al.* Phase II study of high-dose epirubicin in non-small cell lung cancer. *Eur J Cancer* 1990, **26**, 1140–1141.
14. Nielsen D, Jensen JB, Dombernowsky P, *et al.* Epirubicin cardiotoxicity: a study of 135 patients with advanced breast cancer. *J Clin Oncol* 1990, **8**, 1806–1810.
15. Alexander J, Dainiak N, Berger HJ, *et al.* Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiocardiography. *N Engl J Med* 1979, **300**, 278–283.
16. Schwartz RG, McKenzie WB, Alexander J, *et al.* Congestive heart failure and left ventricular dysfunction complicating doxorubicin therapy. Seven-year experience using serial radionuclide angiocardiography. *Am J Med* 1987, **82**, 1109–1118.
17. Torti FM, Bristow MM, Lum BL, *et al.* Cardiotoxicity of epirubicin and doxorubicin: assessment by endomyocardial biopsy. *Cancer Res* 1986, **46**, 3722–3727.
18. Shepherd FA, Feld R, Blackstein M, *et al.* Administration of high dose bolus epirubicin (EPI) is not associated with increased cardiotoxicity. *Proc Am Soc Clin Oncol* 1989, **8**, 335.

Eur J Cancer, Vol. 27, No. 10, pp. 1234–1238, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

MMAF for Advanced Gastric Cancer

Heather Anderson, J. Howard Scarffe, Malcolm Ranson, Arvind G. Kamthan, Mark Dougal, Sarah A. Russell, Michael J.S. Wilkinson and D. Graham Ostick

65 patients with metastatic gastric carcinoma were treated with a combination of methotrexate 1.5 g/m² with 5-fluorouracil 1.5 g/m² on day 1 and doxorubicin 30 mg/m² with mitomycin 4 mg/m² on day 14. Cycles of chemotherapy were repeated every 4 weeks. The overall response rate was 29% with 6% complete responses and 23% partial responses. Prognostic factors that individually affected response were Karnofsky performance ($P < 0.002$), and site of the primary tumour ($P < 0.007$). Multivariate analysis showed that only increasing Karnofsky performance ($P = 0.01$) and disease status ($P < 0.02$) (patients with recurrent tumours responding better than patients with postoperative residual disease and those with inoperable disease) were important in predicting response to therapy. The overall median survival was 7 months. All 4 patients with a complete response are alive in remission at 13, 28, 48 and 52 months from the date of starting chemotherapy. Univariate analysis identified increasing Karnofsky performance ($P < 0.0001$), response to chemotherapy ($P < 0.02$) and higher serum albumin ($P < 0.03$) as prognostic indicators for survival. Multivariate analysis, of pretreatment factors and day 14 full blood count showed that only Karnofsky performance ($P < 0.0001$) and day 14 platelet count ($P < 0.03$) were shown to predict survival, higher platelet values being associated with decreased survival.
Eur J Cancer, Vol. 27, No. 10, pp. 1234–1238, 1991.

INTRODUCTION

SURGERY IS the usual treatment for patients with gastric cancer. However, only half of the patients undergoing a laparotomy are suitable for surgery and still fewer are able to undergo curative resection [1]. The prognosis following the diagnosis of inoperable gastric cancer is poor with a median survival of only 4 months [2, 3]. The median survival of patients with operable tumours is 10–17 months. The 5-year survival was reported to be 6–10% in studies of more than 1000 patients [4].

Patients with inoperable or metastatic gastric carcinoma show a modest response rate to chemotherapy. Single agent therapy is associated with a response rate of 21% for 5-fluorouracil (5-FU), 24% for mitomycin and 22% for doxorubicin [5].

A combination of 5-FU, doxorubicin and mitomycin (FAM) showed a response of 50% [6]. However, a review of 12 studies using FAM has shown a response rate of 33% in 453 patients [4].

Methotrexate and 5-FU have been shown to have synergy when given sequentially [7]. The combination of these two drugs with doxorubicin (FAMTX) was reported to have a response rate of 63% and a median survival of 22 months for responders. 48% of responders were reported to be alive at more than 37 months [8, 9].

We have evaluated a regimen that has included the sequential use of methotrexate and 5-FU in addition to doxorubicin and mitomycin (MMAF) in patients with inoperable, postoperative residual or recurrent adenocarcinoma of the stomach. The aims were to assess toxicity and determine the response rate, duration of response and survival.

Table 1. Patients' characteristics

No. of patients	65
Male	48
Female	17
Age (yr) median (range)	58 (21–70)
Karnofsky performance median (range)	70 (50–90)
Symptoms	
Weight loss	54
Abdominal pain	39
Dysphagia	21
Dyspnoea	12
Melaena	4
Sweating	3
Haematemesis	1
Signs	
Local disease	50
Lymphadenopathy	38
Intra-abdominal	27
Other sites	7
Both	4
Liver metastases	18
Pleural effusion	8
Ascites	7
Lung metastases	3
Bone metastases	3
Median cycles of chemotherapy (range)	3 (1–6)

PATIENTS AND METHODS

Adults aged ≤70 years with a proven histological diagnosis of inoperable or recurrent gastric or gastro-oesophageal adenocarcinoma were eligible for the study if they had evaluable disease, a Karnofsky performance status of ≥50% [10], normal urea and electrolytes and a creatinine clearance of ≥50 ml/min.

At presentation patients had the following investigations performed after a physical examination, full blood count, erythrocyte sedimentation rate (ESR), biochemical profile, liver function tests [gamma glutamyl transferase (γGT) and lactate dehydrogenase (LDH)], creatinine clearance and a chest radiograph. Patients with tumour masses that were not measurable clinically were assessed by pretherapy and post-therapy computed tomography (CT). Photographs and other investigations were performed as clinically indicated. Response and toxicity were assessed according to standard criteria [11].

Therapy

On day 1 patients were admitted for methotrexate 1.5 g/m^2 given as an intravenous bolus followed by bolus 5-FU 1.5 g/m^2 1 h later. On day 14 patients were treated in the outpatient clinic with doxorubicin 30 mg/m^2 and mitomycin 4 mg/m^2.

In the 24 h before methotrexate therapy, patients were given 3 g oral sodium bicarbonate every 3 h for eight doses. Patients received 1 litre 0.9% saline together with 1 litre of 1.4% sodium bicarbonate infused via a Y-set over 4 h. 5-FU was given as a bolus exactly 1 h after the methotrexate. Folinic acid 15 mg/m^2 was given every 6 h for 72 h starting 24 h after the methotrexate, with the first dose being administered intravenously.

Methotrexate levels were taken routinely at 24 h. If the level was >150 ng/ml (3.4 × 10^{-7} mol/l) the test was repeated until this level was obtained and patients given extended folinic acid rescue.

Cycles of therapy were repeated at 4-weekly intervals if the leucocyte count was ≥ 3.0 × 10^9/l and the platelet count ≥ 100 × 10^9/l. Three courses were given before reassessment. Therapy was discontinued if the tumour progressed. In the presence of tumour response or stable disease MMAF chemotherapy continued for a total of six courses.

Dose modification

If serum albumin was < 26 g/l the methotrexate and 5-FU doses were each decreased to 1 g/m^2. Large pleural effusions or ascites were drained prior to therapy. If it was not possible to tap an effusion methotrexate and 5-FU were each reduced to 1 g/m^2. On day 15 if the leucocyte count was ≤ 2 × 10^9/l or the platelet count ≤ 75 × 10^9/l, chemotherapy was delayed by 1 week.

Statistical methods

The effects of variables on survival and response duration were analysed by calculating Kaplan–Meier curves which were then compared using the logrank test [12]. Cox regression

Table 2. Factors analysed for effects on response and survival by univariate analysis (logrank test)

Age
Sex
Histology
Time from diagnosis
Pretreatment
Haemoglobin
Albumin
Aspartate transaminase
Alkaline phosphatase
Lactic dehydrogenase
Creatinine clearance
Site of primary tumour
Weight loss
Lymphadenopathy
Karnofsky performance
Local invasion
Disease status—inoperable, postoperative residual disease, recurrent disease
Day 14 platelet and leucocyte counts

Table 3. Estimated response rate to chemotherapy from logistic regression analysis model using KP and disease status

	Postoperative residual	Inoperable tumour	Recurrent disease
KP 50,60	1	3	16
70	6	20	64
80,90	18	46	84

KP = Karnofsky performance score.
%.

Correspondence to H. Anderson.
H. Anderson, J.H. Scarffe, M. Ranson and A.G. Kamthan are at the CRC Department of Medical Oncology; M. Dougal is at the Department of Medical Statistics; S.A. Russell is at the Department of Radiology; M.J.S. Wilkinson is at the Department of Surgery, Christie Hospital, Manchester M20 9BX; and D.G. Ostick is at the Department of Surgery, Bolton District General Hospital, Bolton, U.K.
Revised 24 June 1991; accepted 26 June 1991.

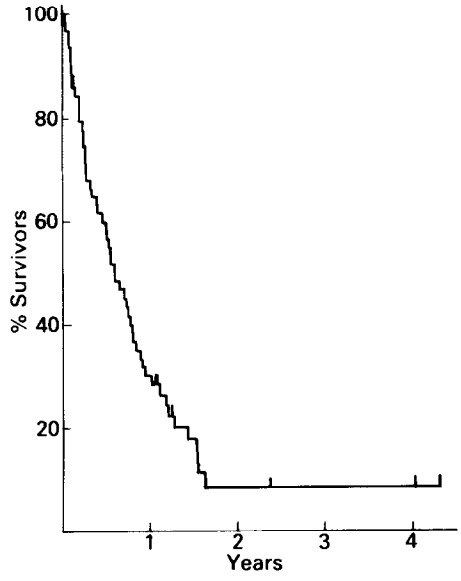

Fig. 1. Overall survival for all patients.

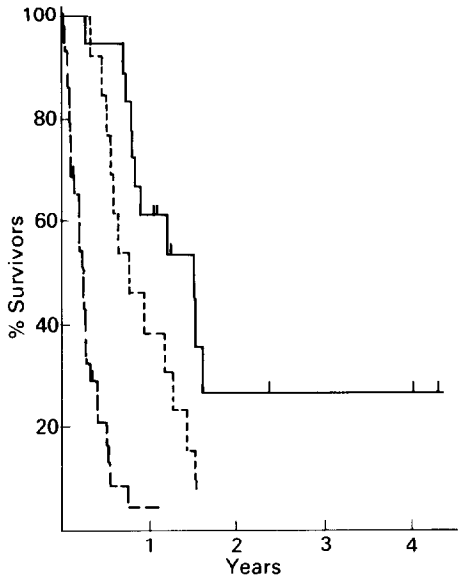

Fig. 3. Survival according to response: —— = complete/partial response, ----- = stable disease, - - - = no response. $P < 0.0001$.

analysis was used to identify prognostic factors for response and survival [12].

RESULTS

65 consecutive patients received MMAF therapy. Patients' characteristics are summarised in Table 1. 48 men and 17 women entered into the study. The median age was 58 years (range 21–70) and the median Karnofsky performance (KP) status was 70% (range 50–90%). At the time of chemotherapy 43/65 (66%) had inoperable disease, 12/65 (18%) had recurrent tumour, 9/65 (14%) had postoperative residual disease and 1 patient had refused surgery.

The main symptoms at the onset of therapy were weight loss 55/65 (85%), abdominal pain 39/65 (60%), dysphagia 21/65 (32%) and dyspnoea 12/65 (18%). Major gastrointestinal haemorrhage was present in 5/65 (8%) patients.

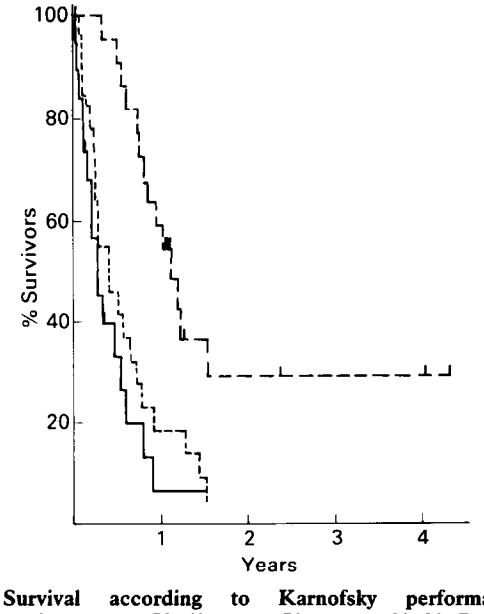

Fig. 2. Survival according to Karnofsky performance at presentation: —— = 50, 60; ----- = 70, - - - = 80, 90. $P < 0.001$.

Response to therapy

The median number of cycles of chemotherapy received was three (range 1–6). 42 patients completed three or more courses of chemotherapy. 19 of 65 (29%) patients responded to therapy with 4 (6%) patients achieving a complete response and 15 (23%) a partial response. Univariate analysis of 18 variables (Table 2) showed that KP and the site of primary tumour both had a significant influence on the likelihood of response. 1 of 19 (5%) patients with a KP of 50–60% responded compared with 6/24 (25%) with a KP of 70% and 12/22 (55%) with a KP of 80+ (Pearson χ^2, $P < 0.002$). The site of the primary tumour was important with more distal tumours responding to therapy (Pearson χ^2, $P < 0.007$). 3 of 20 (15%) with cardio-oesophageal primary tumours, 6/24 (25%) with proximal gastric tumours, 6/17 (35%) with distal gastric tumours and 4/4 with linitis plastica responded to therapy. Excluding patients with cardio-oesophageal primary tumours, the response rate was 16/45 (28%). Repeat analysis excluding patients with linitis plastica showed no statistical significance ($P = 0.36$) between site of primary tumour and response. The median duration of response was 7 months.

Multivariate analysis of prognostic factors for response showed that only KP ($P = 0.01$) and disease status ($P < 0.02$) (inoperable, postoperative residual disease or recurrent disease)

Table 4. Toxicity (WHO grade)

	WHO grade toxicity				
	0	1	2	3	4
Nausea/vomiting	0	13 (20)	29 (45)	22 (34)	1 (2)
Mucositis	20 (31)	13 (20)	29 (45)	3 (5)	0 (0)
Diarrhoea	50 (77)	11 (17)	2 (3)	2 (3)	0
Leucocytes	8 (12)	6 (9)	10 (15)	27 (42)	14 (22)
Platelets	46 (71)	3 (5)	5 (8)	4 (6)	7 (11)
Infection	7 (11)	33 (51)	12 (18)	8 (12)	5 (8)

No. (%).

predicted response to chemotherapy. Patients with recurrent tumour responded to chemotherapy better than patients with postoperative residual disease or those with inoperable tumours. Table 3 shows the estimated response rate to MMAF chemotherapy as predicted from the logistic regression (Cox multivariate) analysis. The predicted response rates varied from 1% for patients with KP 50–60% and postoperative residual disease to 84% for patients with KP 80–90% and recurrent disease.

Survival

The overall median survival was 7 months (Fig. 1) from the start of chemotherapy. Univariate analysis of prognostic factors for survival has shown that longer survival was associated with a higher KP score ($P < 0.0001$), response to therapy ($P < 0.02$) and higher serum albumin ($P < 0.03$).

The median survival according to KP 80–90% was 13 months, KP 70% 4 months and KP 60–70% 3.5 months (Fig. 2). The median survival according to response is shown in Fig. 3; it was 18 months for responders, 9 months for patients with stable disease and 4.5 months for non-responders. All 4 patients who achieved a complete response are alive and disease-free at 13, 28, 48 and 52 months from the date of chemotherapy.

The multivariate analysis showed that decreasing KP ($P < 0.0001$) and higher day 14 platelet counts predicted decreased survival ($P < 0.03$).

Toxicity

Toxicity is summarised in Table 4. All patients experienced alopaecia which was WHO grade 3 in 52% of patients. All patients experienced nausea and 52/65 (80%) had vomiting; however, this was WHO grade 3 in 22 (34%), and grade 4 in 1 (2%) patients.

A sore mouth was reported on at least one occasion by 45 (69%) patients. WHO grade 2 mucositis was seen in 29 (45%) and WHO grade 3 in 3 (5%) patients. 15 (23%) patients had at least one episode of diarrhoea.

Oral antibiotics were prescribed to 22/65 (34%) and intravenous antibiotics to 15/65 (23%) patients. WHO grade 4 leucopenia developed in 14/65 (22%) patients. Blood transfusions were given to 28/65 (43%) patients.

Delays in chemothereapy due to myelotoxicity

A total of 239 cycles of chemotherapy were given. Dosage delays due to myelosuppression occurred in 21/239 (12%) day 1 treatments, and 76/239 (32%) day 14 treatments. Further analysis of day 14 delays showed that this percentage was similar for all cycles of treatment.

DISCUSSION

MMAF chemotherapy was associated with a response rate of 29% and an overall median survival of 7 months. 4 patients are alive in complete remission at 13 months, 28, 48 and 52 months from the start of chemotherapy. The response rate was similar to that of FAM [4], and the overall survival equivalent to that of patients receiving other combination chemotherapy regimens for metastatic gastric cancer perhaps with the exception of combination therapy using etoposide, doxorubicin and cisplatin (EAP) or FAMTX [13, 14].

This paper has identified useful prognostic factors for patients with gastric cancer. The Karnofsky performance status strongly correlated with response to chemotherapy and survival on both univariate and multivariate analysis. On univariate analysis the site of the gastric primary was shown to significantly affect the response to therapy, however this factor was lost on multivariate analysis where Karnofsky performance and disease status prior to chemotherapy alone could predict response to therapy. The best prognostic group were patients with KP 80–90% and recurrent gastric carcinoma. This group had a predicted response rate of 84% to MMAF chemotherapy. Multivariate analysis of prognostic factors for survival showed that increasing Karnofsky performance and lower day 14 platelet count could predict improved survival.

The initial paper from Klein using FAMTX reported a response rate of 63% in 30 patients and a median survival which had not been reached [8]. The latest report of this study shows a response rate of 58% in 116 patients and an overall median survival of 9 months with a median follow-up of 4 years [15]. The EORTC has conducted a phase II study of 5-FU, doxorubicin and methotrexate in the same doses as that used by Klein and obtained a response rate of 33% in 31 patients and an overall median survival of 6 months [16].

22% of patients treated with MMAF developed WHO grade 4 leucopenia. However, there were no toxic deaths. FAMTX has been reported to be associated with toxic death in 3 patients who died of drug-related causes, and 5 patients in this report required haemodialysis [15]. The EORTC have conducted a randomised phase III trial of FAM versus FAMTX to compare response rate and toxicity. The results have shown that there was a superior response rate with FAMTX (41% versus 9% for FAM) and significantly superior median survival (42 versus 29 weeks). The response rate for FAM was lower than expected. Patients' characteristics were similar except that inoperable patients with metastatic disease comprised 49% FAM patients versus 36% patients treated with FAMTX. Toxicity was similar [17].

In conclusion, the addition of sequential methotrexate to 5-FU, doxorubicin and mitomycin (MMAF) did not improve the response rate or survival compared with FAM chemotherapy.

1. Giles GR. Staging and prognostic determinations of gastric cancer. In: Preece PE, Cuschieri A, Wellwood JM, eds. *Cancer of the Stomach*. London, Grune and Stratton, 1986, 89–105.
2. Gilbertson VA. Results of treatment of stomach cancer. *Cancer* 1969, **23**, 1305–1308.
3. Lumpkin WM, Crow RL, Hernandez CM, Cohn I. Carcinoma of the stomach; a review of 1035 cases. *Ann Surg* 1964, **159**, 919–932.
4. MacDonald JS, Steele S, Gunderson LL. Cancer of the stomach, In: Devita VT, Hellman S, Rosenberg SA, eds. *Cancer. Principles and Practice of Oncology*. Philadelphia, Lippincott, 1989, 765–799.
5. LeChevalier T, Smith FP, Harter WK, Schein PS. Chemotherapy, combined modality therapy for locally advanced and metastatic gastric cancer. *Semin Oncol* 1985, **12**, 46–53.
6. MacDonald JS, Wooley FV, Smythe T, Ueno W, Hoth D, Schein PS. 5-fluorouracil, adriamycin and mitomycin C (FAM) combination chemotherapy in the treatment of advanced gastric cancer. *Cancer* 1979, **44**, 42–47.
7. Bertino JR, Sawicki WL, Lindquist CA, Gupta BS. Schedule-dependent antitumour effects of methotrexate and 5-fluorouracil. *Cancer Res* 1977, **37**, 327–328.
8. Klein HO, Wickramarayake PD, Dieterle F, Mohr R, Oekermann H, Gross R. High dose methotrexate, 5-FU and adriamycin for gastric cancer. *Semin Oncol* 1983, **10**, 29–31.
9. Klein HO, Wickramanayake PD, Famolch GR, Mohr R, Oerkermann H. 5-FU, adriamycin and methotrexate combined protocol (FAMeth) for treatment of metastasized gastric cancer (abstr.). *ESMO* 1984, **150**.
10. Karnofsky DA, Burchenall JH. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod CM, ed. *Evaluation of*

Chemotherapeutic Agents. New York, Columbia University Press, 1949, 191–205.
11. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting the results of cancer treatment. *Cancer* 1981, **47**, 207–214.
12. Cox DR. Regression models and life tables. *J Stat Soc* 1972, **(B) 34** 187–220.
13. Wils J, Bleiberg H. Current status of chemotherapy for gastric cancer. *Eur J Cancer Clin Oncol* 1989, **25**, 3–8.
14. Wilke H, Preusser P, Fink U, *et al*. New developments in the treatment of gastric carcinoma. *Semin Oncol* 1990, **17** (Suppl 2.), 61–70.
15. Klein HO. Long term results with FAMTX (5-FU, adriamycin and methotrexate) in advanced gastric cancer. *Anticancer Res* 1989, **9**, 1025–1026.
16. Wils J, Bleiberg H, Dalesio O, *et al*. An EORTC gastrointestinal group evaluation of the combination of sequential methotrexate and 5-FU combined with adriamycin in advanced measurable gastric cancer. *J Clin Oncol* 1986, **4**, 1799–1803.
17. Wils JA, Klein HO, Wagener DJT, *et al*. Sequential high-dose methotrexate and 5 fluorouracil combined with doxorubicin—a step ahead in the treatment of advanced gastric cancer: a trial of the European Organisation for Research and Treatment of Cancer Gastrointestinal Tract Cooperative Group. *J Clin Oncol* 1991, **9**, 827–831.

Eur J Cancer, Vol. 27, No. 10, pp. 1238–1242, 1991.
Printed in Great Britain

0277-5379/91 $3.00 + 0.00

Influence of Pretreatment Clinical Characteristics on the Response Rate to Mitomycin/Vindesine/Cisplatin (MVP) in Unresectable Non-small Cell Lung Cancer

Marcello Riggi, Pierre Ruffie, Sabine Voisin, Isabelle Monnet, Hubert de Cremoux, Jean Claude Saltiel, Michel Martin, Laurence Vergne, Jocelyne Huet and Esteban Cvitkovic for ATTIT (Association pour le Traitement des Tumeurs Intra-Thoraciques)

The authors report their experience with the MVP (mitomycin/vindesine/cisplatin) regimen of the Memorial Sloan-Kettering Cancer Center (MSKCC) which showed the highest response rate in non-small cell lung cancer (NSCLC). The aim was to respect the original reported schedule to appreciate its activity, because the same drug combination with dose and schedule variations used by other investigators has failed to reproduce the original report results. 82 consecutive previously untreated patients with unresectable and/or metastatic NSCLC received mitomycin (8 mg/m^2 days 1, 29, 71), vindesine (3 mg/m^2, days 1, 8, 15, 22, 29, 43, 57, 71) and cisplatin (120 mg/m^2, days 1, 29, 71), with evaluation on day 71. 24 objective responses were noted (29%) (2 complete response/22 partial response) (95% CI 19%–39%), without differences according to histology. Differences in median survival were noted according to the performance status and type of response. Overall survival rates in responding patients were similar to those noted with the original schedules. Analysis of selection criteria showed that there were more patients with bone ($P < 0.01$) or liver metastases ($P < 0.05$), less women ($P < 0.001$) and less adenocarcinoma ($P < 0.001$) than the MSKCC trial. A dose intensity analysis showed only a minimal difference in the average weekly doses of vindesine (10% lower than MSKCC trial: 1.8 mg/m^2 vs. 2.25 mg/m^2). Disease improvement, a subjective response criterion used in the MSKCC trial, was probably underestimated in the current study. We conclude that the potential benefit of chemotherapy with a three-drug combination in NSCLC is greatest in patients with stage IIIa and IIIb disease or stage IV disease with a good performance status and a low metastatic volume.
Eur J Cancer, Vol. 27, No. 10, pp. 1238–1242, 1991.

INTRODUCTION

THE ROLE of chemotherapy in inoperable non-small cell lung cancer (NSCLC) is still contested and many doubts have been raised about its usefulness. After initial positive reports, controlled trials have failed to confirm the response rate and an improvement in survival [1–4], but recent trials have proven some value, especially in low volume or non-metastatic disease [5].

The current most frequently reported combinations in NSCLC contain cisplatin and a vinca alkaloid, and yield response rates of around 25% [6, 7]. The addition of mitomycin to the cisplatin–vindesine regimen (MVP), was reported to signifi-