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Original Paper

A Phase I/II Evaluation of Metoclopramide as a Radiosensitiser in Patients with Inoperable Squamous Cell Carcinoma of the Lung

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The feasibility of administering metoclopramide (MCA) as a radiosensitizer has been evaluated in 23 patients with a pathological or cytological diagnosis of a squamous cell carcinoma of the lung, clinically evaluated as inoperable. All patients received 40–60 Gy radiotherapy fractionated into 1.8 Gy fractions 5 times per week (Monday–Friday). Two MCA treatment regimens were used: (i) MCA at 2 mg/kg administered by intravenous infusion 1–2 h prior to radiotherapy 3 times per week (Monday, Wednesday, Friday); and (ii) MCA at 1 mg/kg administered by intravenous infusion 1–2 h prior to radiotherapy 5 times per week (Monday–Friday). 11 of the 23 patients treated with radiotherapy and MCA had none to mild pneumonitis or fibrosis and another 8 of the 23 had moderate levels. No patient had their therapy interrupted due to radiation-related side-effects. The MCA-related side-effects were as expected, i.e. 78% of the patients experienced sedation/tiredness and 48% expressed restlessness/anxiety symptoms. Both the total dose and serum levels of MCA were significantly associated to the MCA side-effect profile. Tumour response, duration of tumour response and survival were significantly positively correlated to the total and weekly doses of MCA administered to the patients during their radiotherapy treatment. These favourable phase II data have justified the initiation of a phase II/III randomised multicentred trial being carried out in Europe to evaluate MCA as a radiosensitiser.

Key words: metoclopramide, radiosensitiser, lung cancer, phase I/II trial, squamous cell carcinoma
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INTRODUCTION

NON-SMALL cell lung cancer constitutes up to 80% of all lung cancer cases. Most of these patients (i.e. 60–75%) are inoperable, making chemo- and radiotherapeutic approaches the only alternatives. However, despite aggressive chemo- and radiotherapy approximately two thirds of the patients with non-small cell lung cancer die from intrathoracic recurrent tumours [1–6]. The most common form of non-small cell lung cancer is squamous cell carcinoma, and patients with inoperable disease have the worst prognosis [1–5].

Metoclopramide (MCA) is an N-substituted benzamide with affinity for the dopamine (D_2) and 5-hydroxytryptamine (5-HT_3) receptors [7, 8]. Because these receptors have been shown to be involved in mediating emesis, MCA has experienced wide clinical use as an anti-emetic drug, preventing nausea and vomiting [9].

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Recently, our laboratory has shown that MCA can increase the tumour cytotoxicity of cisplatin and ionising radiation in immunodeficient mouse model systems using xenografted human squamous cell carcinomas of the head and neck [10–12]. The endpoint of evaluation was area under the growth curve for tumours treated either with radiation or cisplatin in single dose regimens, or the same regimens combined with MCA at a dose of 2 mg/kg. In another study, evaluating the importance of time when administering MCA in relation to the radiation treatment, data on tumour response showed the drug needed to be given before the radiation to obtain increased tumour toxicity [13]. In addition, MCA has been shown to enhance the cytotoxicity of 1,3-bis(2-chloroethyl)-1-nitrosourea in brain gliomas in rats [14].

Contrarily, acute radiation damage to normal tissue in mice was not increased by MCA. Acute skin reactions in 129-type mice using one or two fractions of radiation was not increased by adding MCA, nor was bone marrow toxicity measured as $LD_{50/30}$ [13].

The mechanism of action of MCA as a chemo- and radiosensitiser is not completely known, although two potential radiosensitising properties have been demonstrated; namely that MCA can increase the level of DNA damage and inhibit DNA repair in the presence of radiation [15]. These properties have also been shown for a wide variety of nicotinamide and benzamide analogues that can radiosensitise [16], although other effects on tumour blood flow are believed to be involved in their radiosensitising properties *in vivo* [17–19]. The relative safety of MCA in the clinic, combined with compelling preclinical data, motivated our research group to evaluate this drug as a radiosensitiser. This phase I/II evaluation reports on the toxicity of MCA in relation to total or weekly doses and serum concentration levels when administered according to a radiosensitising dose schedule over a 4–6 week period.

PATIENTS AND METHODS

Patients

Patients considered inoperable due to medical reasons or with non-resectable, non-distant-metastatic squamous cell carcinoma of the lung and referred to the Department of Oncology, Lund University Hospital, for radiotherapy from January 1991 until November 1993, were entered into this study. The study was approved by the ethical committee of the Medical Faculty of the University Hospital in Lund and by the Swedish Medical Products Agency. Patients were recruited into this study in a consecutive manner. A total of 23 patients were included and their baseline characteristics were: age 52–81 years, 21 males and 2 females, 3 with stage I disease, 5 with stage IIIa disease, 13 with stage IIIb disease, and 2 had recurrent tumours 1 and 1.5 years after primary surgery involving resection of stage I tumours. Staging of the tumours were done according to the tumour-node-metastasis (TNM) classification [20]. All computed tomography (CT) scans and X-rays were evaluated by a radiologist within the research group.

All patients had a Karnofsky performance status of 70% or greater. All patients with primary tumours were examined by bronchoscopy, 7 patients were staged by mediastinoscopy and 4 patients were considered inoperable during thoracotomy. 18 of the patients with primary tumours had biopsy proven squamous cell carcinomas and 3 others had cytologically proven squamous cell carcinomas. The 2 patients with recurrent tumours were verified as having squamous cell carcinomas by fine needle aspirates of the tumour recurrence. Bronchoscopy was positive in 19 of the 21 patients with primary tumours. The tumours were located in the right lung of 14 patients and in the left lung of 9 other patients. Pulmonary vital capacity varied between 2.1 and 4.7 l while the forced vital capacity ranged between 1 and 3.1 l. 18 of the patients were considered inoperable due to tumour extension and 5 were inoperable because of medical considerations.

Radiotherapy treatment

Two different radiotherapy schedules were chosen: (i) 40–45 Gy in 22–25 fractions with 1.8 Gy per fraction for those patients with advanced age, poor performance status or who developed progressive disease outside the radiation field during radiotherapy or (ii) 56–60 Gy in 32 fractions with 1.8–2.0 Gy per fraction for all other patients included. All treatments were given once daily, five times per week (Monday–Friday) with X-ray energies of 4–8 MV, with the exception of one patient treated with 10 MV for the last 16 Gy. No treatment gaps were intended for either treatment group. However, for some of the patients (9/16) in the 56–60 Gy dose group, a recovery period without treatment was necessary. The rest period was between 2 and 25 days. In 4 cases, the rest period was inserted due to high age of the patient (76, 78, 80 and 80 years of age, rest period 11, 10, 18 and 13 days), 2 patients were considered and planned for 40 Gy but, due to shrinkage of tumour, a boost was later planned and a rest period was necessary for a new CT-scan, dose planning and simulation (rest period 2 and 12 days), and 3 patients had rest periods due to medical reasons after the first 40 Gy (rest period 13, 18 and 25 days).

The gross tumour volume (GTV) included the lung tumour as demonstrated on conventional planar radiographs and CT-scan. The CT-scans were also used to detect metastasis in mediastinal and supraclavicular lymph nodes. From this evaluation, the clinical target volume (CTV) with 1 cm margin added for the primary tumour and 2 cm for the lymph node metastasis in the cranio-caudal direction was defined. All volumes were according to the nomenclature of ICRU 50 [21].

The majority of the patients had a three-dimensional treatment plan based on CT-scans covering the whole volume with sufficient margins, cranial and caudal. The thickness of the CT-slices were 1 cm and they were positioned abutted. The CTV was outlined by the radiotherapist on each CT-slice, and a sufficient margin including patient movement during respiration and set-up inaccuracies were added to give the planning target volume (PTV). The patient outer contour, the PTV and the organs at risk (e.g. spinal cord and healthy lung tissue) then formed a three-dimensional volume in which the dose calculations were performed. The irradiation technique has been, for most cases, two opposed fields applied in the anterior/posterior direction (AP fields) with or without an additional lateral field (approximately 90° and with a beam weight of about 25%) entering from the involved side. The lateral field is applied to increase the dose of the mediastinial part of the PTV to the same level as in the cranial part of the volume, where the two opposed fields gives a higher dose due to the shorter distance between the entrance points. Furthermore, this lateral field will also minimise the treated volume and reduce the absorbed dose to the spinal cord, thus providing space for further radiotherapy for those patients scheduled for the higher total doses of 56–60 Gy. Shrinking fields were used in the high dose group whenever applicable for the last 16 Gy. This was always performed with a highly individualised three-dimensional treatment plan. However, due to the site in the lung, laterally opposed fields were common. All fields were individually shaped during the treatment planning using the beam's eye view facility to allow the dose distribution to conform to the PTV. The shape of the individualised blocks were automatically exported to a block cutting device, and the blocks were moulded in Rose's metal. Inhomogeneity corrections were employed for all treatment plans in this study.

The absorbed dose was specified according to ICRU report 50 [21], either at the isocentre or at a point centrally in the gross tumour volume (GTV). The irradiated lung volumes were minimised as much as possible without any low dose regions in the PTV, and half of the lung volume was kept at least below 20 Gy. Spinal cord dose for these patients was always below a total of 42 Gy.

MCA treatment

A 100 mg/ml sterile infusion concentrate (manufactured by Lundbeck AB and now supplied by Lundbeck AB for Oxigene, New York, U.S.A.) was administered by intravenous (i.v.)

infusion at doses of either (i) 2 mg/kg body weight 1–2 h before radiotherapy on a 3 times per week schedule (Monday, Wednesday, Friday), or (ii) 1 mg/kg body weight 1–2 h before radiotherapy on a 5 times per week schedule (Monday–Friday). These dose schedules were selected because they corresponded well to the maximum tolerated dose of MCA already established in the clinic for its anti-emetic use. Therefore, it was possible to evaluate varying daily doses per treatment and serum concentrations without altering too significantly the total MCA dose. Biperiden hydrochloride (Akineton®) was administered i.v. (5 mg/ml injectable) or orally (2 mg tablets) at a total dose of 2–5 mg as required by patients requesting treatment for MCA-related side-effects. Blood samples were taken immediately before i.v. infusion of MCA for determination of serum MCA baseline levels. The infusion period was 30–45 min and was followed directly (i.e. 0–1 h) by radiotherapy. When patients returned to the ward, approximately 1–2 h after the MCA infusion, blood samples were again taken for serum MCA analyses. The 1–2 h blood samples were drawn 15–30 min postradiation treatment. The number of repeated doses of MCA administered to each patient in the study are presented in Table 1.

Determination of MCA serum levels

The MCA serum levels were determined by high pressure liquid chromatography (HPLC) analysis using modifications of the procedure by Meyer and associates [22]. Briefly, 1 ml aliquots of serum, stored at −70°C prior to analysis, were spiked with 100 μM haloperiodol as an internal standard. The samples were made basic with 100 μl 5 mM NaOH, extracted with chloroform:isopropanol (96:4, v/v), and the chloroform phase dried under nitrogen. The residue was washed with 500 μl chloroform, dried again, and redissolved in 15 μl 100% methanol just before HPLC analysis. The HPLC column was a NUCLEOSIL 120-3C_{18} 30 × 4 mm precolumn (Machery–Nagel, Germany), and the mobile phase consisted of 27% acetonitrile and 73% 10 mM sodium acetate (pH 5.0). The retention times for MCA and the internal standard (haloperiodol) were 0.69 min and 2.70 min, respectively. A 2 min washing phase with 60% acetonitrile followed by 5 min reconditioning of the column was performed between each analysis.

Clinical evaluation endpoints

Since the side-effects of MCA are well known even in high dose therapy [8], no particular efforts were made to requantify these clinical endpoints in this material. The main objective in relation to side-effect recording was an evaluation of the ability of patients to tolerate prolonged treatment schedules of high dose MCA. In this study, the side-effects of MCA were recorded by attending physicians and nurses, and by self reporting of the patients 1–2 h before, during and 3–4 h after drug administration in the hospital. The side-effects recorded were sedation/tiredness, anxiety/restlessness, insomnia, diarrhoea, consti-

Table 1. The side-effects induced by metoclopramide administered i.v. over a 4–6 week period in combination with 40–60 Gy radiotherapy to patients with inoperable squamous cell carcinoma of the lung

Patient-dose (mg/kg)	MCA Number of doses tolerated	Appearance and tolerance of side-effects: Sedation/tiredness	Anxiety/restlessness	Other effects	MCA treatment completed	Treatment of side-effects
A-2	6	Yes	Yes	None	No	Biperiden
B-2	14	Yes	None	None	Yes	None
C-2	12	Yes	Yes	Diarrhoea/ Insomnia	Yes	None
D-2	13	Yes	Yes	Extrapyramidal	Yes	Biperiden
E-2	18	Yes	None	None	Yes	None
F-2	18	Yes	Yes	None	Yes	None
G-2	16	Yes	Yes	Constipation	Yes	Biperiden
H-1	31 (13+18)*	Yes	Yes	None	No	None
I-1	30	Yes	None	None	Yes	None
J-1	31	None	Yes	None	Yes	Biperiden
K-1	32	None	None	None	Yes	None
L-1	29	Yes	None	None	Yes	None
M-1	8	Yes	None	Depression	No	Biperiden
N-2	20	Yes	Yes	None	Yes	Biperiden
O-2	17	Yes	None	Diarrhoea/ Insomnia	Yes	None
P-2	13	Yes	None	Depression	Yes	Biperiden
Q-2	12	None	None	None	Yes	None
R-2	17	Yes	None	Extrapyramidal	Yes	Biperiden
S-2	8	None	None	Diarrhoea	No	None
T-2	11	None	Yes	None	No	None
U-2	12	Yes	None	None	Yes	None
V-2	17	Yes	Yes	None	Yes	Biperiden
W-2	18	Yes	Yes	None	Yes	Biperiden
% Effect or mean ± S.D.	17.6 ± 8.0	78%	48%	35%	78%	44%

*Dose reduced from 1 mg/kg to 0.5 mg/kg as indicated.

pation, depression and extrapyramidal reactions. All side-effects were graded as ± parameters.

Radiation-induced normal tissue toxicity was evaluated by monitoring the acute and late radiation effects according to RTOG/EORTC radiation morbidity scoring criteria [23].

The efficacy of the radiotherapy plus MCA treatment was evaluated using measurement of tumour size before, during and after therapy by analysis of CT scans and chest X-rays. The first evaluation of tumour response was done 4–6 weeks after completion of therapy and then at 3 months intervals. A complete response (CR) was defined as no pathological evidence of tumour in the treated area confirmed by histology. Partial responses (PR) were defined as a reduction of 50% or more in the product of two perpendicular diameters of the tumour. Stable disease (SD) was defined as less than a 50% reduction in the tumour, less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and no new lesions. Progressive disease (PD) was defined as an increase of more than 25% in the product of two perpendicular diameters of any measured lesion.

Survival was measured from the starting date of radiotherapy to the date of death.

Statistics

Statistical analyses have been carried out using the statistical program SPSS (SPSS Inc.). Adverse experience rates were compared by Fisher's exact test. Student's *t*-test was used to compare the quantitative data between two groups. Pearson correlation analyses showed the relationship between weekly or total MCA dose and the tumour response score. Kaplan–Meier analyses were used to calculate mean and median survival.

RESULTS

Radiation side-effects

None of the patients had their radiotherapy interrupted due to radiation-induced side-effects. The radiation morbidity scores for skin, oesophagus, lung and heart are presented in Table 2. The majority of patients expressed none to mild radiation side-effects (i.e. grades 0–1, Table 2) at all organ sites evaluated. There were heart symptoms of tachycardia in 3 patients, but these effects could also be attributed to or influenced by the combined treatment with MCA. Another patient had chest pain which was associated with heart enlargement and pleural/pericardial effusion. This patient was initially treated with furosamide, cortisone, antibiotics and bed rest. Later the patient developed congestive heart failure but he is still alive 38 months after radiotherapy treatment. 11 of 19 patients who had evaluable lung X-rays showed none to mild pneumonitis or fibrosis (i.e. grades 0–1, Table 2). Moderate pneumonitis or fibrosis (i.e. grades 2–3, Table 2) was observed in the 8 remaining evaluable patients.

Table 2. Acute and late radiation effects for patients with inoperable squamous cell carcinoma of the lung treated with radiotherapy plus metoclopramide (MCA)

Scoring grade*	Number of patients Skin	Oesophagus	Lung	Heart
0	13	18	7	15
1	9	4	4	3†
2	0	0	6	0
3	0	0	2	1
4	0	0	0	0
Total‡	22	22	19	19

*Evaluated according to RTOG/EORTC radiation morbidity scoring criteria. †Tachycardia during acute treatment phase could also be related to MCA treatment. ‡Not all patients were evaluable due to progressive disease or data not evaluable.

MCA side-effects

All 23 patients received MCA treatment in hospital. 19 patients were treated as hospital inpatients to allow for regular close observation of MCA-induced side-effects. 4 of the 23 patients received the MCA treatment on an outpatient basis. The side-effects from MCA administration were mainly central nervous system related (Table 1). The mean (± S.D.) number of doses for the 23 patients receiving MCA in combination with radiotherapy was 17.6 ± 8.0. Sedation/tiredness, anxiety/restlessness and other symptoms (i.e. diarrhoea, insomnia, constipation, depression and extrapyramidal reactions) were experienced in 78, 48 and 35%, respectively. Moreover, 78% of the patients completed the MCA treatment course and 44% required Biperiden treatment to alleviate the MCA side-effects (Table 1). However, the Biperiden-relieved side-effects were primarily of psychological origin and not life threatening. These side-effects were also analysed in relation to the total dose of MCA administered. Both sedation/tiredness and an overall side-effect score, calculated as a total of all the types of symptoms evaluated, significantly related to the total dose of MCA received by the patients (Table 3). Other side-effect categories reported in Table 1, such as completion of MCA treatment and Biperiden treatment, could not be related to the total dose of MCA administered (Table 3).

Tumour response and survival

The average tumour area at the start of radiotherapy with MCA treatment was 31.1 ± 19.3 cm^2. 3 of the 23 patients were still alive at the time of this analysis (September, 1994). One of the 23 patients was not evaluable for tumour response due to death before the first follow-up examination. Complete response (CR) was achieved in 2/22 (9%) patients, partial response (PR) in 9/22 (41%), stable disease (SD) in 9/22 (41%) while 2/22 (9%) showed progressive disease (PD). The mean time to local tumour

Table 3. Metoclopramide (MCA) side-effects analysed according to the total dose of MCA administered to patients with inoperable squamous cell carcinoma of the lung receiving radiotherapy plus MCA

Side-effect endpoint	MCA total dose <2000 mg	≥2000 mg	*P*-value
Sedation/tiredness	7/12 (58%)	11/11 (100%)	0.04*
Anxiety/restlessness	5/12 (42%)	6/11 (55%)	0.84*
Other symptoms (Table 2)	3/12 (25%)	4/11 (36%)	0.67*
Completed treatment	8/12 (67%)	10/11 (91%)	0.32*
Biperiden treatment	4/12 (33%)	6/11 (55%)	0.41*
Doses tolerated	17.3 ± 10.4	17.6 ± 4.3	0.95†
Side-effect score‡	1.25 ± 0.9	1.91 ± 0.5	0.04†

*Fisher's exact test, two-tailed. †*t*-test, two-tailed. ‡Sedation/tiredness + anxiety/restlessness + other symptoms indicated in Table 1 were scored as none = 0 and yes = 1 and the sum calculated as an overall indication of MCA side-effects.

Table 4. Tumour response and survival in patients with inoperable squamous cell carcinoma of the lung treated with metoclopramide (MCA) and radiotherapy

Parameter	Clinical category: Progressive + stable disease (n = 8)	Clinical category: Partial + complete responses (n = 11)	P-value*
Radiation dose (Gy)	52.5 ± 8.1	50.4 ± 8.2	0.582
Tumour response† × duration index‡	3.8 ± 3.1	31.7 ± 27.0	0.006
Survival (months) (mean ± S.E.M.)	9.9 ± 1.9	18.5 ± 3.4	0.044
MCA total dose (mg) (mean ± S.D.)	1820 ± 291	2273 ± 543	0.048§
MCA weekly dose (mg)	367 ± 44	431 ± 92	0.061§

*Two-tailed t-test. †Progressive disease = 0, stable disease = 1, partial response = 2, and complete response = 3. ‡Sum of the tumour response × duration of response = index. §Pearson correlation coefficients comparing either MCA total or weekly doses to tumour response gave $r = 0.52, P < 0.02$ and $r = 0.52, P < 0.02$, respectively.

progression was 10.8 ± 8.5 months (CR+PR+SD, n = 20), local tumour progression occurred in 59% of the patients, and distant metastases were observed in 68%. Average survival (Kaplan–Meier) was 15.3 ± 2.4 (S.E.M.) months, and survival was also significantly associated with the tumour response. In addition, both these endpoint parameters were statistically related to the total and weekly doses of MCA (Table 4). Contrarily, age, tumour size or stage, total dose of radiotherapy, Biperiden treatment and MCA side-effects could not be shown to significantly influence either tumour response or survival.

Two different treatment schedules were used; namely 2 mg/kg 3 times per week and 1 mg/kg 5 times per week. Therefore, weekly and total MCA doses were calculated so that the patients treated with the 1 and 2 mg/kg dose level could be pooled for statistical analysis of a phase II effect. When the patients who were excluded from the analyses were only those that did not complete at least 10 MCA treatments (3 of 23, Table 1) or when tumour response data was missing (1 of 23), both the weekly and total doses of MCA related to tumour response, duration of tumour response index and survival (Table 4).

Serum levels of MCA

The 1–2 h serum levels of MCA were determined by HPLC analysis for 22 of the 23 patients treated with radiotherapy and MCA. The 1–2 h MCA serum level was selected so as to correspond as close as clinically possible to the actual period of radiation treatment. The data in Table 5 clearly show that, regardless of whether MCA was administered on a 5 times or 3 times per week schedule, the drug clears well from peripheral circulation following repeated injections. The 1–2 h MCA serum levels of patients treated with radiotherapy and MCA could be significantly correlated to the known side-effects of MCA, but not to the clinical outcome endpoints of tumour response or survival. The MCA side-effect score was calculated as sedation/tiredness plus anxiety/restlessness plus other symptoms (see Table 1) as none = 0 and yes = 1, and the sum calculated as an overall indication of MCA side-effects. The MCA side-effect

Table 5. The average metoclopramide (MCA) serum levels during radiotherapy plus MCA treatment of patients with inoperable squamous cell carcinoma of the lung. Patient A had no MCA serum levels determined

Patient	MCA dose (mg/kg)	MCA serum levels: 0.5–1 h preinjection n	0.5–1 h preinjection μM ± S.D.	1–2 h postinjection n	1–2 h postinjection μM ± S.D.
B	2.0	—	—	3	6.17 ± 1.61
C	2.0	—	—	4	4.25 ± 0.48
D	2.0	—	—	4	2.98 ± 0.49
E	2.0	—	—	6	5.58 ± 1.96
F	2.0	—	—	6	3.92 ± 1.07
G	2.0	—	—	6	5.80 ± 1.84
H	0.5	—	—	6	0.58 ± 0.10
I	1.0	12	0.15 ± 0.06	12	0.83 ± 0.32
J	1.0	11	0.11 ± 0.08	11	1.12 ± 0.24
K	1.0	10	0.23 ± 0.17	10	1.40 ± 0.47
L	1.0	7	0.51 ± 0.19	8	2.10 ± 0.57
M	1.0	3	0.13 ± 0.04	3	1.11 ± 0.27
N	2.0	6	0.45 ± 0.29	6	3.55 ± 0.85
O	2.0	7	0.20 ± 0.21	7	3.04 ± 0.69
P	2.0	4	0.61 ± 0.47	4	5.10 ± 1.10
Q	2.0	1	0.15	1	1.73
R	2.0	1	0.19	1	1.92
S	2.0	1	0.40	1	2.71
T	2.0	2	0.20 ± 0.04	2	2.06 ± 0.12
U	2.0	1	0.12	1	2.00
V	2.0	2	0.20 ± 0.01	3	3.24 ± 1.02
W	2.0	1	0	1	2.04

score (± S.D.) in patients with a serum level of MCA less than 2.5 μM was 1.18 ± 0.75 whereas in patients with a serum level of MCA above 2.5 μM the score was 1.91 ± 0.70 ($P = 0.03$). The 2.5 μM level was chosen as the cut-off point so that there would be equal numbers of patients in each group.

DISCUSSION

This study was designed to examine the feasibility of using MCA as a radiosensitiser in the clinic. The radiation-induced side-effects were within the expected range for treatment with radiation alone (Table 2; refs [24–26]). The MCA side-effects of sedation/tiredness and restlessness/anxiety were also similar to those observed when the drug has been administered as an anti-emetic, although the patients' abilities to complete treatment were lower (Tables 1, 3; refs [8, 27]). It should be noted that, unlike MCA treatment of patients for nausea and vomiting, patients receiving MCA according to a radiosensitising regimen do not routinely experience short term relief of any symptoms. This point may explain a slightly higher intolerance to the drug compared to the use of MCA as an anti-emetic. Moreover, the long-term follow-up period (44 months) of a 23 patient study has allowed a phase II evaluation [28]. The fact that the total and weekly doses of MCA received with the combined radiotherapy MCA treatment significantly related to tumour response, duration of tumour response index and survival (Table 4), is supportive of a phase II effect of MCA as a radiosensitiser.

Radiotherapy to an absorbed dose of 40–60 Gy is still the most common treatment of inoperable non-small cell lung cancer [25], even though clear cut effects on survival are lacking [24]. Currently, there is no standard efficacious therapy available for inoperable non-small cell lung cancer. Reasons for treatment failure of this type of cancer include (i) the presence of undetected distant metastases at the time of administration of the radiation therapy, (ii) the location of lung tumours near radiosensitive organs such as oesophagus, heart and spinal cord, and (iii) the difficulty in assessing tumour volume due to tumour-induced secondary changes such as atalectasia and infections in the lung. However, there have been reports in the literature of clinical success using high doses of radiation [26, 29–31] as well as by combining the radiotherapy with cisplatin [32, 33], MIC (mitomycin, ifosfamide, cisplatin) [34] and misonidazole [35] therapies. Other approaches such as accelerated hyperfractionated radiotherapy [35] and three dimensional dose planning [31] have also experienced some success in the clinic. MCA offers a clear clinical alternative approach to these treatment modalities because it is an adjunct to radiotherapy with no known independent cytotoxic mechanism that may contribute to the cytotoxic agent side-effect profiles.

MCA provides a new clinical opportunity for controlling tumour growth because: (i) it has been shown to have potentially unique mechanisms of action not yet evaluated in the clinic (e.g. DNA repair inhibition and increasing DNA damage [15, 36]) compared to other extensively studied radiosensitisers such as nitroimidazoles and DNA base analogues [37], (ii) it has been used safely in the clinic for more than 15 years at doses that can radiosensitise in animal models and the side-effects are mild and well known [8], and (iii) animal models have shown that it radiosensitises tumour tissue but not normal tissue [11, 13]. Because MCA has also been shown to sensitise cisplatin and BCNU chemotherapies [10, 12, 14], the clinical relevance to non-small cell lung cancer is far reaching. For example, the potential of MCA to sensitise both cisplatin and radiation when used in combined therapy seems to be a logical challenge for the future in order to control this type of lung cancer. Therefore, based on the significance of the phase I/II data reported in this study, a randomised multicentre phase II/III study has been initiated in several European countries to evaluate radiotherapy (60 Gy ± MCA) for the treatment of inoperable non small-cell lung cancer.

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