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Phase II study of Edatrexate in stage III and IV non-small-cell lung cancer*

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Summary. A total of 49 patients with advanced, previously untreated non-small-cell lung cancer (NSCLC) were treated with a new antifolate, Edatrexate (10-ethyl-10-deaza-aminopterin; 10-EdAM). Patients received 80 mg/m^2 weekly for 12 weeks, and responders received a further 6 cycles at 2-week intervals. Dose reductions were carried out for haematological toxicity and mucositis. Response was assessed prior to each treatment according to WHO criteria. Among the 45 evaluable patients, 6 [13.3%; 95% confidence interval (CI), 6%–26%] achieved a partial response (PR) and 9 (20%; 95% CI, 11%–34%) showed a minor response (MR; 25%–50% reduction in the sum of 2 perpendicular tumour diameters). In those receiving four or more cycles of treatment, the PR and MR rates were 17.6% and 26.4%, respectively. The resultant toxicity mainly constituted skin rash, mucositis and myelosuppression. Edatrexate is active against NSCLC and produces toxicity profile similar to that of methotrexate.

Introduction

Few drugs produce response rates exceeding 15% in patients with non-small-cell lung cancer (NSCLC) [1]. The most active combination chemotherapy regimens are associated with response rates of up to 50% [2, 12]. Recent reports [4] have suggested that even less effective regimens may produce a survival benefit in localised but inoperable disease. Active agents are therefore needed in attempts to improve the survival of patients with this common disease. Similarly, active drugs whose toxicity is low or manageable might be of value as palliative treatment in more advanced disease.

Edatrexate (10-ethyl-10-deaza-aminopterin) is a water-soluble antifolate that was originally introduced by DeGraw and co-workers [3]. It differs from methotrexate in the substitution of a carbon for the N10 nitrogen (10-deaza-aminopterin) and in ethylation at this site. Evidence has been presented for increased uptake of this drug into tumour cells and lower influx into intestinal mucosal cells as compared with methotrexate. Its efficacy in animal tumours and human xenografts is superior to that of methotrexate [7, 11]. A phase II study in NSCLC [8] indicated activity, with 6 of 19 patients showing a major tumour response. The present study represents a further phase II assessment of Edatrexate conducted in a larger group of patients with previously untreated NSCLC in an attempt to extend these encouraging observations.

Patients and methods

A total of 49 patients with histologically confirmed NSCLC who had not previously undergone chemotherapy were recruited into the study between May 1988 and August 1990. All histology was reviewed at the major coordinating centres. All patients were required to have inoperable, locally recurrent or metastatic disease that was either measurable or evaluable, to be 75 years of age or younger and to exhibit a performance status of 0, 1 or 2 (WHO scale) as well as adequate pre-treatment renal function (serum creatinine, 120 μmol/l) and liver function (bilirubin, <20 μmol/l). Subjects were excluded if they had central nervous system metastases, a history of any previous malignancy (other than basal-cell skin carcinoma or in situ cervical cancer), a significant volume of third-space fluid, active infection, congestive cardiac failure or significant arrythmia.

The treatment schedule consisted of 12 weekly bolus injections of 80 mg/m^2 Edatrexate (Ciba-Geigy Ltd.) into a fast-running intravenous line of normal saline. No pre- or post-hydration or anti-emetic therapy was given. Haematological dose modifications were based on white cell and platelet counts (Table 1). In patients who developed mucositis or macular rashes, treatment was withheld until recovery, after which the dose was reduced by 25% for grade 1 or 2 toxicity (WHO scale) or by 50% for grades 3 or 4 toxicity. On the completion of 12 weekly courses, individuals with responding or stable disease were given a further 6 courses at 2 week intervals. Patients were reviewed weekly for response

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Table 1. Dose reductions for haematological toxicity

WBC ($\times 10^9$/l)	≥4 100%	≥3 {75%	≥2 Delay 1 week {75%	≤1.9 Delay 1 week {50%
Platelets ($\times 10^9$/l)	≥100 100%	≥75 {75%	≥50 Delay 1 week {75%	≤49 Delay 1 week {50%

Table 2. Patients' characteristics

Number		49
Sex (M/F)		35/14
Mean age (range)		63 (39–74) years
WHO performance status:		
	0	24
	1	18
	2	7
Disease stage:		
	III	36
	IV	13
Histology:		
Squamous-cell carcinoma		22
Adenocarcinoma		17
Large-cell (undifferentiated)		10
Disease assessment:		
Measurable		23
Evaluable		22
Measurable and evaluable		4
Previous radiotherapy		0
Previous surgery		2

and toxicity, and treatment was discontinued when objective evidence of disease progression or severe toxicity was found.

The first response assessment was made at 4 weeks or after the completion of at least four injections, but all patients were evaluated and included in the analysis. The data reported herein represent the maximal response achieved by any individual. Patients who developed progressive disease prior to the 4th week of treatment were considered to be non-responders. Response to therapy was assessed at each treatment, and chest X-rays were subsequently reviewed independently. Response was defined as follows:

1. In measurable lesions (lesions measurable in two perpendicular diameters), a complete response was defined as the disappearance of all measurable disease for longer than 4 weeks and the absence of new lesions. A partial response represented a reduction of ≥50% in the sum of the perpendicular diameters of all measurable lesions that lasted for 4 weeks or longer, the duration being measured from the beginning of the therapy. A minor response (MR) was defined as a reduction of 25%–50% in the sum of the perpendicular diameters of all measurable lesions and the absence of new lesions. Stable disease represented a reduction of <25% or an increase of <25% in the sum of the perpendicular diameters of all measurable lesions and the absence of new lesions. Progressive disease was defined as the appearance of new areas of malignancy, an increase of >25% in the sum of two diameters of any lesion as compared with either the size at entry or, for patients who responded, the size at the time of maximal regression.

2. In evaluable lesions (non-measurable lesions), a complete remission (CR) was defined as the disappearance of all clinical evidence of disease for a minimum of 4 weeks as determined by physical examination and chest X-ray. A partial remission (PR) represented a definite decrease in the size of the evaluable lesion that lasted for at least 4 weeks,

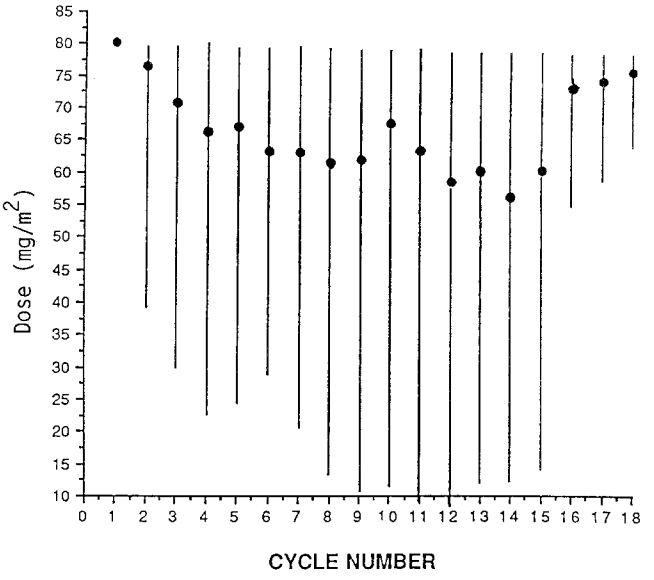

Fig. 1. Mean dose of Edatrexate (*filled circles*) and range (*vertical lines*) for all patients according to chemotherapy cycle

the lack of a simultaneous increase in any other lesion and the absence of new lesions. Stable disease (SD) was defined as any regression of lesions that did not fulfill the criteria for a complete or partial remission and the absence of evidence of progressive disease. Progressive disease (PD) represented the unequivocal worsening of any evaluable lesion or the appearance of new lesions.

Informed consent. The study was approved by the individual ethical committees of the participating hospitals. Informed consent was obtained in written or verbal form according to local institutional practise.

Statistical consideration. Confidence intervals (CI) were calculated according to the method of Simon [9].

Results

From May 1988 to August 1990, a total of 49 patients were entered into the study. The pre-treatment characteristics of the patients are listed in Table 2. In all, 22 patients had squamous-cell carcinoma; 17, adenocarcinoma; 6, large-cell undifferentiated carcinoma; 3, undifferentiated carcinoma; and 1, large-cell anaplastic carcinoma. None of the patients had previously been treated with radiotherapy, and two individuals had undergone prior surgery. Figure 1 shows the mean dose and range given for each course of Edatrexate.

Response

The response rates are outlined in Table 3. Of the 34 patients who received ≥4 treatments, 6 (17.6%) achieved a PR and 9 (26.4%) showed an MR. Of the 15 subjects who completed <4 cycles, 6 developed PD, 5 withdrew because of toxicity (none of these patients had responded by the time of withdrawal) and 4 refused treatment after 1, 2, 3 and 3 cycles, respectively. The latter

Table 3. Response of patients with stage III and IV NSCLC to treatment with Edatrexate

Response	Number	%	95% CI
Patients receiving ⩾4 treatments:			
Total	34		
PR	6	17.6	8%–33%
MR	9	26.4	15%–43%
SD	10		
PD	9		
Patients receiving <4 treatments:			
Total	15	–	–
Progressive disease before 4 cycles	6	–	–
Toxicity (all non-responders)	5	–	–
Refused treatment (1, 2, 3, and 3 cycles)	4[a]	–	–
Evaluable patients:			
Total	45		
PR	6	13.3	6%–26%
MR	9	20.0	11%–34%
SD	15		
PD	15		

[a] These 4 patients were excluded from the overall analysis

Table 4. Percentage of patients developing toxicity[a]

	WHO grade			
Toxicity	0	1	2	3
Mucositis	30	9	40	21
Skin rash	61	12	21	6
Nausea and vomiting	53	21	20	6
Infection	79	2	15	4
Alopecia	83	17	0	0
Leucopenia	86	6	2	6
Thrombocytopenia	94	0	2	4

[a] The worst WHO-grade toxicity recorded during any treatment cycle

4 patients were deemed to be inevaluable. For the 45 evaluable patients, the overall PR rate was 6/45 (13.33%; 95% CI, 6%–26%) and the MR rate was 9/45 (20%; 95% CI, 11%–34%). The mean duration of PRs was 18.3 weeks and the range was 6–39 weeks (6, 8, 10, 13, 34 and 39 weeks, respectively).

Toxicity

Table 4 shows the worst toxicity encountered during the treatment according to WHO grade. The most common toxicity was mucositis, with 70% of patients experiencing grades 1–3 at some point in their treatment. In all, 39.6% of patients developed rashes whilst on treatment. Of the five individuals who failed to complete four cycles of treatment due to toxicity, four had received two doses of drug and one had received a single dose; in each case, rash and/or mucositis was the reason for withdrawal. Of the patients who received more than four treatments, two were taken off study due to mucositis alone and two others discontinued treatment due to a combination of genital/mouth ulceration and macular rashes. Overall, in 54% of patients, treatment was delayed for at least 1 week due to toxicity. Following the first episode of toxicity, appropriate dose reductions were carried out to prevent further toxic effects.

One death was considered to be directly attributable to Edatrexate administration. This patient became severely myelosuppressed, exhibiting thrombocytopenia (platelet count, 31 $\times$ 10^9/l), leucopenia (WBC, 1.2 $\times$ 10^9/l) and severe cellulitis and blistering on the right shin. In another case, treatment was discontinued due to a combination of thrombocytopenia and mucositis along with exacerbation of peripheral vascular disease. One patient who had completed one course of treatment developed atrial fibrillation, but the connection of this episode with Edatrexate administration was uncertain. Transient elevation of aspartate transaminase values was seen in 12 individuals but was not accompanied by clinical symptoms. Toxicity was directly related to the 1-h serum concentration measured during the first cycle of Edatrexate [5], and levels above 3 ng/ml always resulted in clinical toxicity or the need for dose reduction.

Discussion

The PR rate obtained in the present study was lower than that reported by Shum et al. [8]. A comparison of age and performance status revealed little difference between the two studies. Only 35% of our patients had adenocarcinoma as compared with 50% in the previous series. On the other hand, only 26% of our patients exhibited detectable metastases as compared with 70% in the series of Shum et al. [8]. Our multi-institution group drew patients from a wide area of London, including regions of considerable social deprivation, although case selection for the present study was also influenced by the ability of individuals to travel for weekly treatment. Doses were reduced only when patients developed toxicity. In the study of Shum et al. [8], dose escalations were implemented (10 mg/m^2 every 2 weeks) until toxicity was encountered. On the other hand, these authors halved the dose after the occurrence of grade 1 toxicity, but they did not report details on the dose received. These factors together with the variability in interpretation of the responses on chest X-rays probably account for much of the difference between the response rate reported herein and that obtained in the single-institution study. Taken together, the two studies give a PR rate of 12/68 (17.6%; 95% CI, 10%–28%). This may represent an underestimation of the activity of Edatrexate, since we observed 9 MRs that were clinically and radiologically definite. As in the investigation by Shum et al. [8], the main dose-limiting toxicity in the present study was myelosuppression and mucositis. Skin rash can be troublesome during Edatrexate administration [13], and this side effect appears to be different from that caused by methotrexate both in its clinical manifestation and in that it is sometimes unrelated to other toxicities.

Rates of response to methotrexate in NSCLC have been variable. Many reports are old and involve variable response criteria, often in pre-treated patients, as well as widely differing dose schedules [1]. Altogether, treatment

with methotrexate has been associated with a response rate of <15% [6]. It therefore seems possible that Edatrexate is more active than methotrexate. The analogue, which was introduced because of its favourable uptake characteristics [10], is heavily polyglutamated in cells. The two phase II studies in NSCLC do not provide proof of the superiority of Edatrexate over methotrexate but are highly suggestive of this conclusion.

We have shown (unpublished data) that the dose of Edatrexate can be greatly increased without producing toxicity by the administration of folinic acid at 24 h. This strategy may facilitate the incorporation of Edatrexate into multiple-drug combinations, although further study of its effectiveness as a single agent given on different schedules in the presence and absence of folinic acid will be necessary. The toxicity of Edatrexate is related to the 1-h plasma level [5]; monitoring of this single parameter may enable the safe use of Edatrexate, including dose escalation.

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