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# Phase II study of XR 5000 (DACA), an inhibitor of topoisomerase I and II, administered as a 120-h infusion in patients with non-small cell lung cancer

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**Abstract**

XR5000 is a tricyclic carboxamide-based cytotoxic agent that binds to DNA by intercalation and stimulates DNA cleavage by inhibition of both topoisomerase I and II. The aim of this study was to evaluate the antitumoral activity and safety profile of XR5000 given as second-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). Patients received XR5000 at the dose of 3010 mg/m$^2$ as a 120-h central venous infusion every 3 weeks. The 15 patients (median age 56 years, range 48–71 years) enrolled had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (3 patients), 1 (11 patients) or 2 (1 patient). A total of 32 cycles of XR5000 (median 2, range 1–6) were given to 14 patients. No objective response (assessed according to World Health Organization (WHO) criteria) was documented in the 12 evaluable patients by an external review panel; in 4 out of the 12 patients disease stabilisation was recorded. The following toxicities graded according to the Common Toxicity Criteria (CTC) version 2.0. were observed: one grade 3 and two grade 4 granulocytopenia, one grade 3 and one grade 4 thrombocytopenia, one grade 3 deep venous thrombosis, one grade 3 fatigue, and grade 3 undocumented epileptic seizures which led to death in 2 patients. With only 4 out of 12 patients reaching stable disease when using this dose and regimen, further evaluation of XR5000 in advanced NSCLC is not justified.


*Keywords:* Advanced non-small cell lung cancer (NSCLC); Phase II study; Topoisomerase I and II inhibitor; XR5000

## 1. Introduction

XR5000 {N-[2-(dimethylamino)ethyl]-acridine-4-carboxamide}, formerly known as DACA, is one of a series of tricyclic carboxamide cytotoxic drugs that bind to DNA by intercalation, and acts as an inhibitor of both topoisomerase I and II [1]. This dual inhibition and its activity in preclinical models, including those exhibiting drug resistance mediated by P-glycoprotein or the multidrug resistance protein, make XR5000 an attractive agent for clinical development [2]. The maximum tolerated dose (MTD) of XR5000 given as a short infusion was 800 mg/m$^2$ with pain in the infusion arm precluding further dose escalation. When administered as a 3-h infusion

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on a single day [3] or over 3 successive days [4], the arm pain was still the main toxicity. Myelosuppression was minimal, but dose-related; somnolence or agitation, peri-oral paresthesia and lacrimation were also observed. One patient, who received XR5000 over 3 h through a central venous catheter, also experienced severe chest pain. Accordingly, a subsequent study evaluated XR5000 given as 120-h infusion through a central venous catheter which enabled further dose escalation to 4060 mg/m$^2$. This was associated with grade 4 chest and abdominal pain. The 3010 mg/m$^2$ dose level was well tolerated although vomiting and somnolence were documented with the administration of XR5000 over 120 h.

Lung cancer has become the leading cause of cancer-related mortality in both sexes. Five-year survival rates for patients of stages III A and B no longer curable by local therapies drop to 15 and 5%, respectively. Chemotherapeutic agents available against non-small cell lung cancer (NSCLC) have only a modest anti-cancer activity in the range of 10–30%. Thus, new substances with antitumoral activity against lung cancer are urgently needed. Among the active substances in clinical use are representatives of the classes of the topoisomerase I-inhibitors such as the camptothecins, irinotecan and topotecan, and of the topoisomerase II-inhibitors such as the anthracycline, doxorubicin, and the epipodophyllotoxins such as etoposide [5]. Therefore, the testing of a new substance unifying the characteristics of both classes, i.e. inhibition of topoisomerases I and II, seemed promising. In addition, XR5000 is lipophilic and crosses the blood–brain barrier in preclinical models [6]. Some of the toxicities observed in the phase I trials such as somnolence or agitation, peri-oral paresthesia and lacrimation suggest that XR5000 may also penetrate the central nervous system in man. Thus, lung cancer which is known to be associated with a high tendency to develop brain metastases, is an ideal candidate to potentially profit from this feature of XR5000.

The principle objective of this phase II trial was to define the objective response rate of XR5000 in patients with advanced NSCLC who had received one line of chemotherapy for recurrent disease. Secondary objectives were to determine the duration of any response and to assess the toxicity profile of XR5000 in this setting.

## 2. Patients and methods

### 2.1. Patient selection

The ethical committee of each centre participating in this study approved the study and all patients gave their written informed consent before registration. Patients were eligible if they were at least 18 years of age with histologically- or cytologically-proven NSCLC and recurrent disease presenting with at least one target lesion, which was bi-dimensionally measurable by computed tomography (CT) scans and fulfilled the criteria of target lesions; i.e. besides the primary disease, lymph nodes and/or distant metastatic lesions have to measure at least 2 cm in their largest diameter. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, as well as a life expectancy of at least 3 months, adequate haematological reserve (leucocytes $>3.0\times10^9$/l, platelets $>100\times10^9$/l), normal liver biochemistry (bilirubin $<1.5$-fold upper limit of normal (ULN), transaminases and alkaline phosphatases $\leqslant 2$-fold ULN in the absence of liver metastases and $\leqslant 5$-fold ULN in the case of liver metastases), normal renal function (serum creatinine $\leqslant 150$ μmol/l), clinically normal cardiac function as well as absence of symptomatic brain metastases. Patients were ineligible if they had previously received radiotherapy within the last 4 weeks. The investigational therapy was restricted to the second-line setting. Patients must have received only one line of a platinum-based or platinum-free chemotherapy for metastatic or inoperable locally advanced progressive disease.

### 2.2. Treatment

XR5000 (supplied by Xenova Ltd, Slough, UK) was administered at a dose of 3010 mg/m$^2$ diluted in 250 ml of normal saline. It was delivered as a 120-h (5 day) continuous infusion through an indwelling central venous catheter using an ambulatory pump. Prophylactic antiemetics were given according to local practice. Chemotherapy was repeated every 3 weeks, with each cycle comprising 5 days of XR5000 and 16 days off treatment. Treatment could be delayed by up to 2 weeks if toxicities had not resolved by day 21. Dose modifications for toxicity were not planned.

### 2.3. Patient evaluation

Patients were to be treated until disease progression or unacceptable toxicity occurred or until they or their physician considered further therapy with XR5000 inappropriate. The response was assessed every other course according to the World Health Organization (WHO) criteria [7]. An external review panel assessed the best response for all patients documented by CT scans. The toxicity was graded according to the Common Toxicity Criteria (CTC) version 2.0.

### 2.4. Statistical methods

This was an open-label, non-randomised, multicentre phase II study using a Gehan two-stage design. If at least one clinical response was seen in the first 14 eligible

patients (based on the intent-to-treat principle), the recruitment was to continue to a total of 25 patients. With this design, a chance of erroneously rejecting the drug with a true response rate of 20% after the first 14 patients is 0.044.

## 3. Results

### 3.1. Patient characteristics

From January 2000 to November 2000, 15 patients were entered into this phase II study at six institutions. All patients satisfied the eligibility criteria at entry. The clinical characteristics and prior treatments of the eligible patients at the study entry are shown in Table 1. All but one patient who had been treated with gemcitabine single-agent therapy received a platinum-based combination chemotherapy as first-line treatment for progressive metastatic or locally advanced disease.

### 3.2. Response

14 patients received a total of 32 cycles (median 2, range 1–6). One patient died of progressive disease on the planned day of treatment start and thus never received therapy with XR5000. The median relative dose intensity was 96% (range 76–113%). No dose reduction was performed. 8 out of the 14 patients went off study due to progressive disease. In 4 patients, treatment was stopped due to toxicity. In 1 patient, therapy was stopped due to intercurrent death from an epileptic seizure at home and in a further patient due to pneumonia which was not related to the application of the investigational drug.

No objective responses were observed and the 95% confidence interval (CI) for the estimate of the response rate was (0; 25); thus, the study was closed at the first step. Overall, 4 of the 15 patients showed stable disease, which lasted a median of 16.5 weeks (range 8–31 weeks). 8 patients had disease progression. 3 patients were not assessable; 1 patient died of disease progression prior to the start of treatment with XR5000 and 2 patients died of non-electro-encephalogram (EEG)-documented epileptic seizures in the absence of brain metastases at cycle one.

Table 1
Characteristics of all eligible patients ($n = 15$)

| Variables | |
|---|---|
| Age (years) | |
| Median (range) | 56 (48–71) |
| Sex | |
| Male | 14 |
| Female | 1 |
| Histological subtype | |
| Unknown | 1 |
| Squamous cell | 6 |
| Adenocarcinoma | 4 |
| Large cell undifferentiated | 3 |
| Mixed adenosquamous | 1 |
| Stage of disease | |
| IIIa | 1 |
| IIIb | 5 |
| IV | 9 |
| Performance status (ECOG) | |
| 0 | 3 |
| 1 | 11 |
| 2 | 1 |
| Prior radiotherapy | |
| None | 11 |
| Haematopoietic sites excluded | 2 |
| Haematopoietic sites included | 2 |
| Prior surgery | |
| None | 13 |
| Curative | 1 |
| Other | 1 |
| Prior chemotherapy (one line) | |
| For advanced disease | 15 |

ECOG, Eastern Cooperative Oncology Group.

### 3.3. Toxicity

All 14 patients who started treatment with XR5000 were evaluable for toxicity. Haematological toxicity was extremely mild. Two grade 4 granulocytopenia and one grade 3 granulocytopenia as well as one grade 4 thrombocytopenia and one grade 3 thrombocytopenia were observed. 22% of all 32 cycles administered were associated with grade 3/4 toxicity in 4 patients and with dose delay in 1 patient on two occasions. No febrile neutropenia was documented. The worst non-haematological toxicities were of grade 3 only and are depicted in Table 2. The only other reason for dose delay and finally for dose interruption was a deep venous thrombosis of the jugular, axillar and subclavian left vein (grade 3) probably related to the implanted central venous access device. The event occurred despite the prophylactic application of low molecular weight heparin. In 1 patient, fatigue (grade 3) was judged to be drug-related; brain metastases and transient mental confusion finally resulted in fatal oedema. Neurotoxicity (grade 3) in the form of an epileptic seizure which was declared as possibly drug-related manifested in 1 patient in the absence of brain metastases. The other epileptic seizure reported in a second patient was classified as a non drug-related episode since it happened in a patient with a known history of epilepsy. All other drug-related toxicities, notably alopecia, gastrointestinal toxicity in the form of anorexia, constipation, alteration of taste and conjunctivitis were of grade 2 or less. In 1 patient, a dose interruption was necessary because of transient unexplained thoracic pain of grade 2 which resolved without sequelae. Myocardial infarction or a thromboembolic event could be excluded.

Table 2
Maximal CTC grade 3 toxicities related to XR5000

| Patient no | Toxicity | At cycle | Comments |
|---|---|---|---|
| 4 | Deep venous thrombosis | 2 | Thrombosis of the jugular, axillar and subclavian left vein despite use of prophylactic low molecular weight heparin |
| 10 | Fatigue | 1 | Episode of mental confusion resolved spontaneously; patient had multiple brain metastases |
| 15 | Epileptic seizure | 1 | Generalised tonic/clonic seizure in absence of brain metastases |

CTC, Common Toxicity Criteria, Version 2.0.

## 4. Discussion

XR5000 was selected from a series of acridine-derivatives because of its curative activity against the Lewis lung carcinoma, an experimental lung tumor in mice [1]. Additional cell line experiments performed by Baguley from the Auckland Cancer Society (XR5000 Investigator Brochure, ed. 3, 1998) included seven different lung cancer cell lines and demonstrated comparable activity to etoposide. XR5000 binds to DNA by intercalation and stimulates DNA cleavage by both topoisomerase I and topoisomerase II. In addition, XR5000 is notable for its ability to overcome multidrug resistance *in vitro* induced by the four currently understood processes namely P-glycoprotein pump, multi-drug resistance protein, topoisomerase I and topoisomerase II [8]. In particular, the latter feature should theoretically mean that XR5000 is an ideal candidate for use as second-line treatment. Clinical agents such as etoposide and doxorubicin which target the enzyme topoisomerase II and derivatives of the plant product camptothecin, such as topotecan and irinotecan, which target topoisomerase I have an established role in the treatment of a variety of tumors, among them lung cancer [5].

The disappointing results of this study in which not a single objective response was observed out of 12 evaluable patients and in which only 4 patients experienced stabilisation of their disease as their best response are in clear contrast to all these theoretical assumptions and promising preclinical data. They are in line with other data from a broad phase II programme undertaken by the European Organization for Research and Treatment of Cancer—Early Clinical Studies Group (EORTC-ECSG) in glioblastoma multiforme [9], colorectal cancer [10] and in ovarian cancer [11].

What conclusions can be drawn from this experience? Firstly—and this is certainly no spectacular new insight—clinical results cannot be simply extrapolated from preclinical experiments. Secondly, the results obtained raise the question of whether it was even justified to expect better ones. With regard to the negative experience with glioblastoma multiforme, the pragmatic clinical answer would have been a clear no. With regard to colorectal cancer, irinotecan is the only topoisomerase I-inhibitor which demonstrates a high activity. For lung cancer, the situation presents differently with several of the most effective compounds currently used belonging to the class of inhibitors of topoisomerase I and II. Thirdly, with only 12 out of the 15 patients available for the final response evaluation—1 patient died within the frame of a pre-existing medically controlled epileptic disease from a seizure and a further patient experienced tonic/clonic seizure in the absence of brain metastases and the third patient died of progressive disease on the day of the planned start of treatment—this limited the testing of our investigational agent. Fourthly, it has to be reconsidered whether in advanced lung cancer, new substances should preferably be tested in a first-line approach.

Preclinical data suggest that the drug has a low activity against leukaemic cells [12] and also in the phase I setting only modest and rare haematotoxicity was documented [4]. In our series, no febrile neutropenia was observed. Only 4 patients experienced grade 3/4 haematotoxicity.

The occurrence of severe chest and abdominal pain with XR5000 at a dose of $>3010$ mg/m$^2$ precluded testing the drug at a higher dose in this trial. Nevertheless, it is questionable whether higher doses would have had a higher antitumoral activity. In *in-vitro* experiments on the Lewis lung cell culture, higher XR5000 concentrations caused less cell killing (XR5000 Investigator Brochure, ed. 3, 1998). The exposure of cells to a low drug concentration for an intermediate time period was found to be more cytotoxic than exposure to a high drug concentration for the complementary time period which results theoretically in the same exposure [13]. There are reports in literature supporting a synergistic effect of topoisomerase I and topoisomerase II inhibitors [14,15], whereas other authors have detected a reduced cytotoxicity [16,17]. Whether the latter was a reason for the lack of antitumoral activity in our series is not known.

Grade 3 deep venous thrombosis occurred in one patient, despite prophylactic heparinisation. This drug-related complication was described also in the phase I and phase II programmes [9,10]. The central nervous system toxicity was documented during phase I programmes, partly consisting of unusual but not severe

sensations such as fatigue, drowsiness, loss of body coordination, dys-paresthesia, lacrimation, flushing, alteration of taste or anxiety [4]. Whether the epileptic seizures in the absence and without evidence of brain metastases, respectively, observed in 2 patients are drug-related toxicities is debatable.

In conclusion, XR5000 given by this route and schedule does not have any antitumoral activity in systemically pretreated patients with metastatic or locally advanced NSCLC, and further evaluation of XR5000 in this setting is therefore not justified.

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