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Acknowledgements—We are grateful to J.C. Nicolas and B. Terouane (Unité 58 INSERM, Montpellier, France), Dr C. Besmond (Unité 91 INSERM, Créteil, France) and Dr R. Mazars (URA CNRS 199, Montpellier, France) for methodological advice. We thank Drs F. Laffargue and J.P. Moles for providing human normal and cancer tissues, E. Barrié and M. Egéa for typing the manuscript and L. Proux and C. Rougeot for technical assistance.

This work was supported by the Institut National de la Santé et de la Recherche Médicale, the University of Montpellier 1, the Association pour la Recherche sur le Cancer and the Association Vaincre les Maladies Lysosomales.

Pergamon

European Journal of Cancer Vol. 30A, No. 3, pp. 394–395, 1994

0959-8049/94 $6.00+0.00

0959-8049(93)E0031-K

Phase II Trial of Anaxirone (TGU) in Advanced Colorectal Cancer: an EORTC Early Clinical Trials Group (ECTG) Study

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Anaxirone, a rationally synthesised triepoxide derivative, was given to 46 patients with metastatic colorectal cancer. Good risk patients received 800 mg/m^2 as a rapid intravenous injection every 4 weeks, whereas poor risk patients received 650 mg/m^2. Of 46 patients, 45 were evaulable for toxicity and 42 for efficacy analysis. There were 37/45 patients with poor risk, showing no difference in toxicity as compared to good risk patients. The major toxic effect was myelosuppression with 34% of all patients experiencing grade 3 or 4 leucopenia; thrombocytopenia was less frequent. Locoregional phlebitis occurred in 66% of the patients. There was no objective tumour response to anaxirone in 42 evaluable patients. Only 4 patients achieved stabilisation of the disease lasting maximally up to 248 days. Anaxirone is inactive in metastatic colorectal cancer.
Eur J Cancer, Vol. 30A, No. 3, pp. 394–395, 1994

INTRODUCTION

ANAXIRONE (α-β-TRIGLYCIDYLURAZOL, TGU, NSC-332488) is a rationally synthetised triepoxide derivative which has shown high antitumour activity in five animal tumour models [1]. In clinical phase I investigations, the dose-limiting toxic effect was myelosuppression. Dose-related gastrointestinal toxicity and dose-unrelated mild to moderate phlebitis were also seen [2–4]. This study was undertaken to determine if responses can be achieved with anaxirone in advanced colorectal cancer, and to further characterise the toxic effects of anaxirone in this patient population.

PATIENTS AND METHODS

Eligibility criteria consisted of measurable recurrent or metastatic colorectal disease not amenable to curative surgery and/or radiotherapy, life expectancy of at least 3 months, a WHO-Zubrod ECOG performance status of grade ≤ 2, age ≤ 75 years, pretreatment white blood cell (WBC) count of $\geq 4.0 \times 10^9$/μl, platelet count $\geq 100 \times 10^9$/μl, serum creatinine < 132 μmol/l and bilirubin < 25.6 μmol/l, no prior radiotherapy or chemotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin) and no brain involvement or leptomeningeal disease. The protocol has been submitted and

was approved by an ethical committee, and all patients gave informed consent.

Anaxirone was provided by Asta-Werke (Degussa Pharma Group, Germany) in vials containing 100 and 500 mg anaxirone and 20 and 100 mg D-mannitol, respectively, as a sterile, pyrogen-free lyophilised powder. Good risks patients, defined as a performance status of < 2 and no prior or minimal chemotherapy (less than three cytotoxic drugs) and no prior radiotherapy (extensive pelvic or spinal irradiation), received an initial anaxirone dose of 800 mg/m^2 as a rapid intravenous (i.v.) injection in 200 ml dextrose 5% every 4 weeks. All other patients were considered as poor risk, and received an initial dose of 650–600 mg/m^2. In case of no toxicity, the anaxirone dose could be escalated up to a maximum of 960 mg/m^2. Responses and toxicity were assessed according to the WHO criteria [5].

RESULTS

Thirteen institutions of the EORTC/ECTG accrued 46 patients within 1 year. 45 were evaluable for toxicity and 42 for tumour response. There were 8 good risk patients (four males) with a median age of 66 years (range 57–74) and a performance status of 0–1. The remaining 37 patients (19 males) had a median age of 54 years (range 29–75) and 12 had a performance status of 2. At entry, the following indicator lesions were reported: liver (11 cases), lung (10 cases), lung plus liver (8 cases), lymph nodes (5 cases), abdomen (3 cases), soft tissue (3 cases), skin, lung plus lymph nodes, abdomen plus lymph nodes, soft tissue plus lymph nodes and abdomen plus lung (1 case each). 37 patients had received prior treatment (chemotherapy alone: 27, radio-chemotherapy: 10). Prior adjuvant single-agent fluorouracil was administered to 1 patient without success, and palliative chemotherapy was given to the remaining previously treated patients. Single-agent chemotherapy was administered to 20 patients of whom 19 had received either fluorouracil or the fluorouracil prodrug doxifluridine. Of these 19 patients, 5 had achieved a response (fluorouracil 2, doxifluridine 3). More than three-drug combination chemotherapy had been given to 5 patients. The median time from last treatment to treatment start with anaxirone was 45 days (range 24–263). The only patient with less than a 28-day treatment-free interval (24 days) did not respond to a prior fluorouracil–methotrexate combination.

Anaxirone showed no activity in the 42 evaluable patients, but in the two-dose groups, 4 patients achieved a stable disease for 56–248 days after a median number of two treatment courses (range 1–8). Four good risk patients had a 20% dose increase, and a dose reduction of 25 and 50% was given to 8 and 2 patients, respectively. A 41-year-old woman died during the course of the study of myelosuppression and possible septicaemia. All other patients developed progressive disease.

There was no significant difference in the toxic effects between the good and poor risk patients. The major toxic effect was myelosuppression, with 34% of all patients experiencing grade 3 or 4 leucopenia, and 22% experiencing grade 3 or 4 thrombocytopenia. Lack of recovery (more than 3 months after the last treatment course) from thrombocytopenia was observed in 4 patients who received more than two courses of anaxirone, suggesting a cumulative toxic effect on thrombopoiesis. Nausea/vomiting was observed in 96% of the patients, with 24% experiencing WHO grade 3 or 4. Locoregional phlebitis occurred in 66% of the patients with WHO grade 3 or 4 in 11%.

DISCUSSION

In this phase II study with anaxirone, no responses were observed in 42 evaluable patients with advanced colorectal cancer, including 8 patients with no prior treatment. Patients who received no prior treatment are considered as more likely to respond to a new drug [6]. However, in our most recent trials in colorectal cancer patients, no responses were seen in unpretreated patients either [7,8]. The current phase II strategy of requiring entry of previously untreated patients results in a significant and possibly unnecessary prolongation of most phase II studies in this type of tumour, due to increasing difficulties in accruing unpretreated patients. The difference in response rates between unpretreated and pretreated colorectal cancer patients was reported to range from 5 to 10% [6, 7, 9, 10]. An active drug would, therefore, show antitumour activity, even in patients with limited prior chemotherapy (less than three drugs). Sixty-four per cent of our pretreated patients fit into that particular category. Based on these results, we conclude that anaxirone, as used in this study, has no activity in patients with advanced colorectal cancer.

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Revised 12 July 1993; accepted 19 July 1993.

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