Tallimustine in advanced previously untreated colorectal cancer, a phase II study

CJA Punt[1], Y Humblet[2], E Roca[3], LY Dirix[4], R Wainstein[5], A Polli[6] and I Corradino[6]

[1]University Hospital Nijmegen, Nijmegen, The Netherlands; [2]University Hospital St. Luc, Brussels, Belgium; [3]Gastroenterology Hospital, Buenos Aires, Argentina; [4]University Hospital Antwerp, Antwerp, Belgium; [5]Posadas Hospital, Buenos Aires, Argentina; [6]Pharmacia, Milan, Italy.

Summary Tallimustine is a novel benzoyl mustard derivative from distamycin A with a unique mode of action. It is a DNA minor groove binder and produces highly sequence-specific alkylations. Previous studies have shown significant anti-tumour effects in animal models. We performed a phase II study in previously untreated patients with advanced colorectal cancer, using a schedule of i.v. bolus infusions of 900 μg m^{-2} once every 4 weeks. Seventeen patients were enrolled, and no responses were documented in 14 evaluable patients. Toxicity mainly consisted of a highly selective neutropenia, which warrants further investigation of this agent in combination with myeloid growth factors.

Keywords: tallimustine; DNA minor groove binder; alkylating agent; colorectal cancer

Tallimustine is a synthetic derivative of the antiviral distamycin A, in which a formyl group at the N-terminal position has been replaced by an alkylating benzoyl mustard moiety (Arcamone et al., 1989). Although its mechanism of action is not precisely known, its anti-tumour activity has been attributed to a very limited number of highly sequence-specific alkylations of DNA (Broggini et al., 1995). Tallimustine binds preferentially to adenine–thymine rich sequences in the minor groove of DNA, inhibits the binding of transcription factors that recognise these sequences and specifically inhibits DNA ligase. Unlike classic alkylating agents it does not alkylate guanine N7 but only adenine N3 (Broggini et al., 1991; Coley et al., 1993, Montecucco et al., 1991). Furthermore, it has immunomodulating properties in that it augments T-cell-dependent antibody production (Riganti et al., 1992). It displays potent anti-tumour effects on human and murine tumour cell lines as well as on murine transplated solid tumours and human tumour xenografts (Arcamone et al., 1989; Giuliani et al., 1988; Pezzoni et al., 1991). Tallimustine is cross-resistant with doxorubicin but not with melphalan and cisplatin, and drug resistance is only partially mediated through mdr-1-p170 (Pezzoni et al., 1991; Geroni et al., 1993; Capolongo et al., 1993). The dose-limiting toxicity in phase I studies was a highly selective neutropenia (Sessa et al., 1994; Abigerges et al., 1993; Hageboutros et al., 1994). In these studies clinical responses were documented in mesothelioma, ethmoid adenocarcinoma and ovarian cystadenocarcinoma. Given the paucity of active agents in patients with advanced colorectal cancer, we initiated a phase II study in previously untreated patients to determine the anti-tumour activity of this new agent.

Patients and methods

Inclusion criteria included histologically documented unresectable advanced or metastatic colorectal cancer, no prior systemic treatment with the exception of adjuvant chemotherapy more than 12 months prior to entry, measurable disease parameter(s), no prior radiotherapy on all disease parameters, age $\geqslant 18$ and $\leqslant 70$ years, ECOG performance status $\leqslant 2$, life expectancy $\geqslant 3$ months, WBC $\geqslant 4 \times 10^{9-1}$ l, granulocytes $\geqslant 2 \times 10^{9-1}$ l, platelets $\geqslant 100 \times 10^{9-1}$ l, serum

bilirubin < 1.5 mg dl^{-1}, alkaline phosphatase, ASAT, and ALAT $< 2 \times$ upper limit of normal (in case of liver metastases $< 5 \times$), no signs of brain metastases, no active infections, no second malignancy (with the exception of adequately treated in situ carcinoma of the cervix or squamous cell carcinoma of the skin), no pregnant or breastfeeding women, and written or oral witnessed informed consent.

Tallimustine (FCE 24517, Pharmacia, Milan, Italy) was administered at 900 μg m^{-2} as an i.v. bolus infusion over 3–5 min, once every 4 weeks. Patients were followed weekly for toxicity and every two cycles for response. Full blood counts were determined weekly and twice weekly in the third week of treatment. Toxicity and response were evaluted according to CTC and WHO criteria respectively. Treatment was only continued after 4 weeks when neutrophil and platelet counts were normal (grade 0). When treatment was postponed or, in the case of neutrophil nadir grade 4 for > 7 days or < 7 days but accompanied by fever $> 38.5°C$, the dose in the subsequent cycle was reduced by 25%. The use of colony-stimulating factors was prohibited. No anti-emetic prophylaxis was given during the first cycle, but was allowed in following cycles when clinically indicated. Patients with progressive disease after two cycles were taken off study, and patients with stable disease received a minimum of four cycles. A two-stage design of the study was used in order to permit termination of the study when no responses were documented in the first group of 14 patients.

Results

Seventeen patients were entered into the study. Patient characteristics are shown in Table I. Patients received a median of two (1–4) cycles, the total number of administered cycles was 34. Three patients were not evaluable for response: one patient refused further treatment after one cycle, one patient was taken off study after one cycle as a result of the development of a pelvic abscess and fistulae, one patient died after the second cycle before tumour evaluation had been performed. Of the 14 patients who were evaluable for response, 13 had progressive disease after a median of two (1–4) cycles, and one patient with stable disease after two cycles refused further treatment (total response rate 0%, 95% confidence interval 0–23%). Toxicity mainly consisted of neutropenia (Table II). A total of 13 (76%) patients experienced grade III/IV leucocytopenia and/or neutropenia during 21 (62%) cycles. Three patients developed febrile episodes during neutropenia that resulted in hospital

Table I Patients' characteristics

Male/female	13/4
Median age (years) (range)	58 (43–66)
Median ECOG performance status (range)	1 (0–2)
Localisation of primary tumour	
Colon	9
Rectosigmoid	2
Rectum	6
Localisation of metastatic disease	
Liver	12
Lung	2
Lymph nodes	4
Local recurrence	2
Other	6
Median number of metastatic sites	1 (1–3)
Previous treatments	
Surgery	16
Radiotherapy	4
Adjuvant chemotherapy	1
None	1

Numbers are patients.

Table II Toxicity of treatment

Toxicity	Grade II	Grade III	Grade IV
Leucocytopenia	4	6	4
Neutropenia	1	1	12
Thrombocytopenia	1	0	0
Anaemia	4	2	0
Infection	0	0	3
Nausea[a]	1	2	0
Vomiting[a]	2	1	0
Anorexia	2	2	0
Diarrhoea	1	1	0
Fatigue	1	2	0

Numbers are patients, maximum toxicity per patient is given. Toxicity according to CTC criteria. [a]No prophylactic antiemetics were administered during the first cycle.

admissions for treatment with i.v. antibiotics. Grade IV neutropenia occurred between days 13 and 17 after the start of treatment and had a median duration of 4 (range 2–9) days. Of the 14 patients who received at least two cycles, toxicity-related dose reductions and treatment delays were performed in one (7%) and two (14%) patients respectively. In these 14 patients no cumulative effect on bone marrow toxicity was seen. Platelet toxicity occurred in only one patient (grade 2). One patient developed symptoms of arterial insufficiency of the left leg together with hypotension and anuria 13 days after the second administration of tallimustine. He also had afebrile grade IV neutropenia, which lasted only 2 days. Despite vigourous treatment with anticoagulants, pressor agents and i.v. antibiotics he died 11 days later as a result of thromboembolic complications resulting in multiorgan failure, confirmed by autopsy. A relation with tallimustine was thought unlikely.

Discussion

Tallimustine appears to be an attractive cytotoxic agent because of its unique mechanism of action, its potent preclinical anti-tumour activity in vitro and in vivo and its lack of non-haematological toxicity. However, we found no activity in patients with advanced colorectal cancer. Studies in other types of cancer are ongoing. Toxicity consisted of a highly selective neutropenia, which confirms the data obtained from phase I studies (Sessa et al., 1994; Abigerges et al., 1993; Hageboutros et al., 1994). A concentration-dependent inhibition of human myeloid progenitor cells has been demonstrated (Volpe et al., 1993). The striking absence of platelet toxicity as well as the low incidence of manageable non-haematological toxicities makes this agent a very attractive candidate for combination with myeloid growth factors.

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