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Results of a Phase II Trial with Cystemustine in Advanced Malignant Melanoma. A Trial of the EORTC Clinical Screening Group

V. Urosevic,[1] Ph. Chollet,[1] A. Adenis,[2] J. Chauvergne,[3] P. Fargeot,[4] H. Roche,[5] P. Kerbrat,[6] M.A. Lentz,[7] P. Fumoleau[8] and B. Chevallier[9]

[1]Centre Jean Perrin, 58 rue Montalembert, B.P. 392, 63011 Clermont-Ferrand Cedex 1; [2]Centre Oscar Lambert, Rue Frédéric Combemale, B.P. 307, 59020 Lille Cedex; [3]Fondation Bergoinie, 180 rue de Saint-Genès, 33076 Bordeaux Cedex; [4]Centre Georges-François Leclerc, 1 rue du Professeur Marion, 21034 Dijon Cedex; [5]Centre Claudius Regaud, 20–24 rue du Pont-Saint-Pierre, 31052 Toulouse Cedex; [6]Centre Eugène Marquis, Rue de la bataille Flandre-Dunkerque, B.P. 6279, 35062 Rennes Cedex, France; [7]EORTC Data Centre, Avenue E. Mounier, 8311, 1200 Bruxelles, Belgium; [8]Centre René Gauducheau, Site Hospitalier Nord, Boulevard Jacques Monod, 44805 Saint-Herblain Cedex; and [9]Centre Henri Becquerel, Rue d'Amiens, 76038 Rouen Cedex, France

MALIGNANT MELANOMA represents only 2% of malignant tumours [1] and is responsible for 65% of deaths from skin cancer [2]. When distant metastases appear, the patient's survival expectancy falls dramatically to a few months [3]. At this stage of the disease, surgery is rarely curative and radiotherapy is only palliative [4]; the best single agent of chemotherapy is DTIC with an average response rate of 22%, similar to that of interferon alpha 2b in biological approaches to therapy. We report here the results of a phase II study conducted by the EORTC Clinical Screening Group in disseminated malignant melanoma with a new nitrosourea, "cystemustine", at a dose of 60 mg/m^2 every 2 weeks.

Eligibility critera for patients included at least one measurable, metastatic, not previously irradiated target, a WHO performance status (PS) of 0–2, normal white blood cell and platelet count and normal renal and liver function. In addition, no previous chemotherapy was acceptable except DTIC and/or immunotherapy previous to patient inclusion. All patients provided written consent.

Cystemustine was given intravenously at a dose of 60 mg/m^2 infused for 15 min in 100 ml 5% dextrose. The treatment plan consisted of one administration every 2 weeks with a minimum of four injections. The target measurement was assessed before the third and fifth infusions, then every 2 months. In responding or stable patients, the treatment was continued until progression or excessive toxicity, to a maximum of 12 months. The injection was postponed for 1 week, if at day 14 the granulocyte count fell below 1500/μl or the platelet count below 100 000/μl. A WHO grade III or IV thrombocytopenia resulted in a dose reduction to 45 mg/m^2 for the subsequent courses. If the treatment had to be delayed for more than 3 weeks, the patient was withdrawn from the study.

Table 1. Maximal haematological and non-haematological toxicity observed

WHO grade (%)	0	1	2	3	4
White blood cells	13 (59)	2 (9)	7 (32)	—	—
Neutrophils	14 (64)	3 (14)	3 (14)	2 (9)	—
Platelets	17 (77)	1 (5)	3 (14)	1 (5)	—
Nausea/vomiting	9 (41)	5 (23)	7 (32)	1 (5)	—
Diarrhoea	20 (91)	1 (5)	—	—	—
Alopecia	20 (91)	1 (5)	—	—	—
Fever	21 (95)	—	1 (5)	—	—
Others	16 (73)	1 (5)	1 (5)	—	—

25 patients were included, and 3 were ineligible: 2 because of previous treatment limitations, and 1 because of previously irradiated targets. There were 9 men and 13 women, the median age was 54 (range 22–69), 13 patients had a PS of 0, 4 PS1 and 5 PS2, 6 patients had received previous radiotherapy, 5 previous chemotherapy and 5 previous immunotherapy. 22 patients were eligible and evaluable for response and toxicity. 2 had a partial response (28+ and 24+ weeks), 5 had stable disease and 15 had progressive disease, giving an overall response rate of 9% (confidence interval 1.12–29.2%). However, the patient with previously irradiated targets, although ineligible, had a partial response lasting 17 weeks.

The toxicity is given in Table 1. 9% of patients experienced WHO grade 3 toxicity for neutrophils, 5% had grade 3 thrombopenia and 5% had grade 3 nausea and vomiting. No other important toxicity was observed and overall tolerance was good. One responding patient underwent surgical resection of a brain metastasis. A complete pathological remission on this cerebral site was seen at pathological examination.

Cystemustine has limited clinical activity on metastatic malignant melanoma. The response rate was low. Due to the observed low toxicity, a new phase II trial with an increased dose is ongoing to evaluate a possible better antitumour activity.

Correspondence to Ph. Chollet.
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Octreotide Treatment of Chemotherapy-induced Diarrhoea

P. Ginopoulos,[1] Th. Papagiannis,[2] Ch. Safridi,[2] F. Karvelas,[3] K. Spyropoulos,[4] Th. Papadas[5] and Ch. Gogos[2]

[1]Oncology Unit, [2]Internal Medicine Department, [4]Respiratory Unit and [5]ENT Department, University Hospital, Medical School of Patras, Patras; and [3]Surgery Department, "Agios Andreas" Hospital, Patras, Greece

THE AIM of the present study was to investigate the efficacy of octreotide, a somatostatin analogue, in the treatment of diarrhoea caused by 5-fluorouracil (5-FU) chemotherapy.

It has been estimated that 10–15% of patients under 5-FU chemotherapy suffer from gastrointestinal toxicity, including diarrhoea and/or stomatitis, oesophagitis and gastritis [1, 2]. Diarrhoea can sometimes be so severe that not only is chemotherapy interrupted but hydration and electrolyte abnormalities of the patient also have to be corrected, requiring hospital admission. Uncontrollable diarrhoea has so far been treated with antidiarrhoeal drugs, such as loperamide and diphenoxylate but without good results [3, 4]. These drugs act mainly at the level of intestinal smooth muscle fibres causing a reduction in motility and, thus, a reduced frequency of diarrhoea. Possibly, they also play a role in the reduction of gastrointestinal excretions.

In 1990, Kennedy and associates published a study [5] reporting the successful treatment of diarrhoea by the use of octreotide. It has been well demonstrated that somatostatin analogues, especially octreotide, have antidiarrhoeal action [6, 7]. Various studies have been published on the subject of treating severe diarrhoea of patients suffering from AIDS or other syndromes [8, 9].

The exact action of octreotide remains unknown. There are many hypotheses to explain its antidiarrhoeal action [10, 11]. In general, it is known that it interferes with various cell functions resulting in a reduction of gastrointestinal system excretions. More specifically, it is suggested that it can block the adenyl cyclase system and cause reduction of the calcium ion influx into the cell. In addition, it is reported that it can decrease the gastrointestinal motility and also exert an action on the ileocaecal valve that decreases the flow of ileal contents into the caecum.

The side-effect profile of octreotide includes nausea, diarrhoea, abdominal pain and pain at the injection site. Special care should be provided to patients with diabetes, since octreotide can alter blood glucose levels.

The present clinical study was conducted under the Helsinki Principles and local regulations. As far as dosage is concerned, the existing data recommend a dose range of 100–800 μg/day s.c. divided in multiple injections. We used 300 μg/day (divided in three aliquots) for 18 ambulatory cancer patients passing up to 10 stools per day and not requiring hospitalisation for fluid and electrolyte support. 4 patients who passed more than 10 stools per day were admitted to the hospital and received rehydration, electrolyte normalisation and continuous octreotide i.v. administration of 800 μg/day. We observed that diarrhoea tended to be more severe in patients with coexisting mucusitis and leucopenia.

There were 14 male and 8 female patients included in the study, with a mean age of 58 years (range 43–75 years). Seven patients had breast cancer with hepatic and/or pulmonary metastases and received Super FAC (5-FU, doxorubicin, cisplatin) chemotherapy. 13 patients had colorectal cancer with hepatic, pulmonary or lymph node metastases. They received the following chemotherapy regimens: (a) 5-FU at a dose of 600 mg/m^2 for 5 days, (b) leucovorin (LV) at a dose of 500 mg/m^2 for the first day of treatment only and (c) interferon (IFN) alpha-2a (3 patients only) at a dose of 9×10^6 U on days 1, 3 and 5 of treatment. 2 more patients had pancreatic cancer with hepatic metastases and received FAM (5-FU, doxuribicin, mitomycin C) treatment.

Our results show that no patient to whom octreotide was administered, either by the subcutaneous (300 μg/day) or the intravenous route (800 μg/day), showed any side-effect due to octreotide, except 2 patients who had mild abdominal distension. Our treatment response criterion was either complete remission of diarrhoea or reduction to one/day. Treatment was discontinued immediately after diarrhoea resolved without relapse. Of the patients who received s.c. treatment, diarrhoea was resolved in 5 patients (4 with 1–4 bowel movements/day, and 1 with 4–7/day) on day 1, in 5 patients (1 with 1–4 bowel movements/day and 4 with 4–7/day) on day 2, in 7 patients on day 3 and 1 patient on day 4 (all 8 with 7–10 bowel movements/day). Of the patients treated with i.v. therapy, diarrhoea resolved in 1 patient on day 3, 2 patients on day 4 and 1 patient on day 1.

Our study results are similar with those reported by Cascinu and associates [12], although the authors did not mention the number of bowel movements (in comparison with the day of diarrhoea remission, a clinical parameter that we consider significant). In conclusion, the results of the present study indicate that octreotide is a promising agent for the successful control of 5-FU-induced diarrhoea.

Correspondence to P. Ginopoulos, 104A Iroon Polytechniou Str., Patras, Greece.
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