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Control of Chemotherapy-induced Diarrhoea with Octreotide in Patients Receiving 5-Fluorouracil

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Chemotherapy treatment with combination of 5-fluorouracil and leucovorin or interferon alpha determined an incidence of severe diarrhoea of 10 and 20%, respectively. Up to date no treatment for this condition has been defined. 21 patients affected by advanced colorectal cancer and 6 patients affected by advanced pancreatic cancer received octreotide as treatment for severe diarrhoea following chemotherapy with 5-fluorouracil/leucovorin (Machover's regimen) or 5-fluorouracil/interferon (Wadler's regimen) combination. Octreotide was administered by subcutaneous injection of 50 μg twice daily on the first day and 100 μg twice daily on the second and third day. 26 patients had total cessation of diarrhoea: 4 patients within the first day, 6 within the second day and 16 within the third day. 1 patient had no change and after the last administration of octreotide he was treated with loperamide and intravenous hydration. Side effects have been mild. In summary octreotide seems to be an effective agent in the management of chemotherapy related diarrhoea.
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INTRODUCTION

CHEMOTHERAPY RELATED diarrhoea is an uncommon problem in the clinical management of cancer patients but it can reduce patient compliance and sometimes it can be a potentially life-threatening disorder. Furthermore new chemotherapeutic combinations such as 5-fluorouracil (5FU) and leucovorin (LV) or 5FU and alpha interferon (IFN) increased incidence and severity of this side effect [1, 2].

Up to date no treatment for this condition has been defined. Octreotide, a potent long acting analogue of native somatostatin, has been useful in the treatment of secretory diarrhoea related to various diseases such as Zollinger–Ellison syndrome, Verner–Morrison syndrome, the carcinoid syndrome, ileostomy, AIDS and graft versus host disease [3–8].

Recently Kennedy *et al.* published preliminary data on efficacy of octreotide also in the treatment of diarrhoea following 5FU/LV combination or radiotherapy [9].

The current study was undertaken to evaluate the effectiveness and side effects of octreotide in the treatment of patients with diarrhoea following 5FU/LV or 5FU/IFN-α_{2b} chemotherapy.

PATIENTS AND METHODS

Patients with diarrhoea grade III (WHO) following 5FU/LV combination (Machover *et al*'.s regimen [10]: 5FU 370 mg/m^2 intravenous daily for 5 days; LV 200 mg/m^2 intravenous daily for 5 days, every 3 weeks) or 5FU/IFN chemotherapy (Wadler and Wiernik's regimen [2]: 5FU 750 mg/m^2 daily for 5 days followed by weekly administration at the same dose; IFN-α_{2b} 9 million units on days 1, 3 and 5 and then three times per week) were evaluable for therapy with octreotide. They were not previously treated with other antidiarrhoeal drugs and didn't receive any other concomitant treatment for this disorder. No patients had a history of diarrhoea before chemotherapy or were treated with radiation therapy on abdomen. Patients' characteristics are reported in Table 1. Octreotide was administered for 3 days by subcutaneous injection of 50 μg twice daily on the first day and 100 μg twice daily on the second and third day.

Each day of therapy patients were assessed for response as following criteria: complete response, no diarrhoea; partial response < two loose bowel movements per day; no effect, > two loose bowel movements per day. Criteria for partial response were chosen after patients' interview, because quality of life was not affected up to two loose bowel movements per day. At the same time possible side effects of therapy were recorded by medical and nursing staff. Informed consent was obtained from all participants after the nature of the study had been fully explained.

RESULTS

27 patients were treated and all were evaluable. 26 patients had total cessation of diarrhoea: 4 patients within the first day, 6 within the second day and 16 within the third day (Table 2). After the third day no therapy with octreotide was continued without recurrence of diarrhoea or presence of prolonged constipation as confirmed in patients' medical examination before the next course of chemotherapy. 1 patient had no change and after the last administration of octreotide he was treated with

Table 1. Patients' characteristics

No. patients	27
Male/female	17/10
Colon–rectum/pancreas	21/6
Age (median)	56
P.S. (ECOG) (median)	1
Location of confirmed metastases	
Liver	12
Liver as major site	7
Lung	3
Pelvis	3
Other	2

P.S. = performance status.

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Table 2. Results

Days of therapy	1	2	3
Complete response	4	9	26
Partial response	20	16	—
No effect	3	2	1

loperamide and intravenous hydration. Diarrhoea was resolved after a further 6 days. No severe side effects from therapy were noted, except pain at the site of injection in 7 patients during drug administration and transient abdominal pain, about 1 h after octreotide therapy, in 2 patients.

DISCUSSION

Secretory diarrhoea is a prominent feature of 5FU gastrointestinal toxicity [11]. It represents the symptom of mucositis of the last part of gastrointestinal tract. We are not aware of data present in literature about the duration of severe chemotherapy induced diarrhoea. Our experience suggests that almost 6 or more days are necessary to completely control 5FU induced diarrhoea with loperamide or other supportive care. Recently association of 5FU with LV or IFN increased the probability of this side effect with a reported incidence of severe diarrhoea of 10 and 20%, respectively [1, 2, 12–15].

The clinical utility of octreotide in the control of symptoms associated with a number of secretory diarrhoeal disorders is well documented [16]. Although the exact mechanism is unknown, a sharp reduction of luminal fluid flow in the upper jejunun and an inhibition of electrogenic chloride secretion with a stimulation of neutral sodium and chloride absorption may be responsible for the observed effect on stool volume [17]. Furthermore the improvement of diarrhoea might also be related to a suppression of intestine motility by octreotide. It has been shown in fact that this drug is able to prolong mouth–caecum transit time and thus to prolong contact time between luminal contents and mucosal surface [18].

As previously seen, because octreotide is effective in situations of secretory diarrhoea, irrespective of the pathogen it was thought that it might also be useful in the treatment of chemotherapy related diarrhoea.

Preliminary data reported by Kennedy *et al.* seemed to be promising [9]. A total cessation of diarrhoea in 11 colorectal cancer patients treated with 5FU/LV chemotherapy or radiotherapy was obtained.

In our experience all patients but one presented a resolution of diarrhoea without appreciable toxicity.

Since most patients presented resolution of diarrhoea after the third day of therapy our schedule could be the optimal treatment, even if it will have to be confirmed in further studies.

In conclusion we think that these data confirm effectiveness of octreotide and suggest its use in the case of severe diarrhoea after 5FU chemotherapy to increase patient compliance, therapeutic safety and to reduce possible hospitalisation.

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