Octreotide in chemotherapy induced diarrhoea in colorectal cancer : a review article

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Abstract

Background : **Chemotherapy-induced diarrhoea (CID) is well known in cancer management. The risk is greater when the primary cancer is colorectal. This article aims towards assessing the role of octreotide in CID through an extensive literature search.**

Methods : After searching through PUBMED, MEDLINE and the Cochrane library, only those studies which were published over the last 20 years in English and where at least the majority of the cohort were colorectal patients, were included. Two randomized trials, four non-randomized studies and two case-series publications were thus considered.

Results : **It was seen in both the randomized studies, that octreotide had much better outcome as compared to loperamide in treating severe CID. Among 88 patients from the non-randomized studies with severe CID, the primary cancer was colorectal in 79 patients. 61 patients had drug-resistant CID. Within a maximum of 96 hours, octreotide reduced CID by ≥ 2 grades in 91% of 88 patients and in 88.52% patients with drug-resistant CID.**

Conclusion : **Octreotide is effective in treating severe CID, resistant to other modes of treatment. It is associated with a few minor adverse effects. Though expensive, octreotide could be considered as first line medication in CID of grades 3 or above. Its use in lower grades of CID would not be cost effective.** (Acta gastroenterol. belg., **2009**, 72, **289-295**).

Key words : octreotide, chemotherapy induced diarrhoea, octreotide in diarrhoea.

Abbreviations

CID = Chemotherapy induced diarrhoea
5FU = 5 Fluorouracil
LV = Leucovorin
UFT = Uracil
NCI = National Cancer Institute
NICE = National Institute of Clinical Excellence

Introduction

Colorectal cancer is the second commonest cause for cancer related mortality in England and Wales and the third commonest cause in the United States (1). In the UK, there are 30,000 new cases each year, a quarter of which are Dukes C or Stage III at presentation. (*please refer to (a) NICE Guidance on Cancer Services : Improving Outcomes in Colorectal Cancers, Manual Update 2000 and (b) Cancer Stats monograph 2004 - cancer incidence survival and mortality in the UK and EU. Bowel Cancer Statistics. Cancer Research UK ; 2004*). All Dukes C, high risk Dukes B and metastatic colorectal cancers are likely to be considered for either post operative (Dukes B/C) or palliative chemotherapy (Dukes D/ metastatic disease) (2,3). Chemotherapy-induced diarrhoea (CID) is common and could be as high as 82%. Nearly a third of these patients have severe grade 3-4 diarrhoea (Fig. 1), which is frequently responsible for hospitalisation, chemotherapy dose modification and early termination of treatment. Chemotherapy regimens used in adjuvant (4,5) and metastatic (6,7) colorectal disease and respective incidences of CID are summarized in the charts (Figs. 2 and 3). Capecitabine, irinotecan, cetuximab and 5FU bolus regimens are often associated with higher incidences of diarrhoea (8-12). Primary colorectal cancer is an independent risk factor for CID. Other independent risk factors reported in the literature are diarrhoea with chemotherapy in earlier cycles, chemotherapy in summer months (13), older age group females (14,15), dihydropyrimidine dehydrogenase (DPD) deficiency, uridine diphosphate glucoronyl transferase (UGT) deficiency (16-20) and adjuvant chemotherapy as compared to palliative therapy (16). Diarrhoea can cause dehydration, electrolyte imbalance, renal impairment, nutritional deficiency and can have negative impact on the management of cancer itself. Severe diarrhoea decreases patient's tolerance towards chemotherapy often resulting in dose reduction or early termination of the treatment. Increased morbidity increases the cost of care and leads to poorer clinical outcomes. Diarrhoea can be associated with chemotherapy-induced neutropenia, which can be serious or even fatal. The severity of the CID is assessed by the National Cancer Institute (NCI) criteria (16). Dranitsaris and colleagues reported an incidence of 54.2% diarrhoea after the first cycle of chemotherapy in a retrospective study and this resulted in a median dose reduction by 20% and median delay in treatment by 7 days. 32.3% cases in this study needed hospitalisation and their median length of hospital stay was 8 days (21).

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National Cancer Institute Criteria for assessing the severity of chemotherapy-induced diarrhoea				
Grades of CID	Frequency of Diarrhoea	Stoma output	Need for intravenous fluid resuscitation	Interfering with daily activities
1	< 4 times/day	mild	none	None
2	4-6 times/day	moderate	< 24 hrs	None
3	≥ 7 times/day	severe	> 24 hrs	Yes
4	Diarrhoea resulting into life theatening consequenes like haemodynamic collapse or shock.			
5	Death due to consequences of diarrhoea			

Fig. 1. — NCI grading of diarrhoea

Chemotherapy-induced diarrhoea in colorectal cancer in adjuvant selling			
No	Chemotherapy / Regimens	Incidence of CID NCI grade ≤3	Reference / Trial / Citation
1.	FOLFOX 4	11%	MOSAIC trial, Andre T., *et al.* N. Engl. J. Med., 2004 Reference – (4)
2.	FLOX	38%	NSABP trial, Kuebler J.P., *et al.*, J. Clin. Oncol., 2007 Reference – (5)
3.	CapO/OxCap	11%	X-ACT Trial. Twelves C., *et al.* Clin. Colorectal Cancer, 2006 Reference – (9)
4.	Capecitabine + Oxaliplatin (XELOXA)	19%	Schmoll *et al.* Journal of Clinical of Oncology, 2007. January ; 25(1) Reference – (10)
5.	Mayo Clinic Regimen (FU/LV)	16%	
6.	Roswell Park Regimen (FU/LV)	29%	

Fig. 2. — Chemotherapy-induced diarrhoea in colorectal cancer in adjuvant setting

Chemotherapy-induced diarrhoea in advanced / metastatic colorectal cancer			
No.	Chemotherapy / Regimens	Incidence of CID NCI grade ≤3	Reference / Trial / Citation
1.	Capecitabine / Oxaliplatin	16%	Cao Y., *et al.* Journal of Colorectal Disease, 2009 Reference – (11)
2.	5 -FU + Oxaliplatin	12.5%	
3.	OxMdG Regimen	6%	Adams R.A., *et al.* British Journal of Cancer, (2009) 100, 251-8 Reference – (12)
4.	OxMdG + Cetuximab	13%	
5.	XELOX	15%	
6.	XELOX + Cetuximab	25%	
7.	FOLFIRI	14%	Tournigand C., *et al.* GERCOR study, Journal of Clinical Oncology, Jan 2004, 24 (2) Reference – (6)
8.	FOLFOX 6	11%	
9.	FOLFOX 4 + Bevacizumab	7.8%	Emmanouilides C., *et al.* BMC Cancer, 2007, 7 (91) Reference – (7)

Fig. 3. — Chemotherapy-induced diarrhoea in advanced / metastatic colorectal cancer

Aim of the study

Octreotide has often been used to treat CID. In the absence of a fixed protocol, treatment has been purely empirical. This review article aims towards assessing the role of octreotide in CID through an extensive literature search.

Methods and materials

We have searched PUBMED, MEDLINE and Cochrane library for relevant published articles over the last 25 years from 1984 to 2009. The phrases like "octreotide in chemotherapy induced diarrhoea", "octreotide CID", "colorectal cancer CID and

octreotide" and "chemotherapy induced diarrhoea in colorectal cancer and octreotide" were used to search for relevant articles. We included those studies, which were published in English and where the whole cohort or at least a major proportion of it were colorectal cancer patients. We have included two randomized trials, four non-randomized controlled studies and two case series publications in our review. The articles related to patients having chemotherapy solely for cancers other than colorectal carcinoma and solitary case reports regarding use of octreotide or other modes of medications to control CID were excluded. We have also looked at the pharmaco-economic aspects relating to octreotide, its recommended safe dose and its adverse effects in the treatment of CID only.

Results

i) *Octreotide vs other medications in CID*

A randomized trial (22) established the effectiveness of octreotide against loperamide in controlling severe CID (NCI grades 2 and above) in a cohort of 41 patients (68.3% colorectal cancer) ($P < 0.005$). Gebbia *et al.* performed a similar randomized trial (23), where the group of patients receiving octreotide had much better results, compared to those receiving loperamide (Fig. 4). In a prospective non – randomized study (24), colorectal cancer patients with grade 3-4, loperamide resistant CID, were treated with octreotide. In this cohort, nearly 16% of patients had complete resolution of diarrhoea and about 59% experienced reduction of diarrhoea by at least two grades. In the remaining 25% of cases, diarrhoea was reduced by one grade. A similar prospective multicentre trial by Zidan *et al.* (25) in a cohort of patients, (the majority of which were colorectal cancer patients) with severe loperamide resistant CID, octreotide was used as a failsafe and complete resolution of diarrhoea was noted in 94% cases without any major adverse effects. This study did not specify the exact percentage of colorectal cancer patients who were among this complete resolution group. A prospective study (26) reporting the effects of octreotide in a cohort with opioid-resistant CID, demonstrated 94% success rate with no serious side effects. Cascinu *et al.* (27) has reported a better success rate (96.3% complete response within 72 hours of onset of treatment) with octreotide in a cohort of 27 patients (21 patients with advanced colorectal cancer and rest with advanced pancreatic cancer). When we combined the results of all these non-randomized studies, in a cohort of 88 patients (colorectal cancer in 79 out of 88 cases) with severe CID (NCI grades 3 and above), 61 patients (69.32%) with opioids or loperamide resistant CID were treated with octreotide, which was effective in controlling diarrhoea in 54 (88.52%) patients within a maximum of 4 days.

Two case series publications by Rosenoff (28,29) reported successful treatment of severe CID (NCI grades 3 and above), refractory to loperamide and/or diphenoxylate atropine, by octreotide LAR (long acting release preparation). Both these publications demonstrated improvement in patients' quality of life and tolerance towards chemotherapy. No serious adverse effects were reported in either of them.

ii) *Dose of octreotide in CID*

In the absence of fixed dose related guidelines, the use of octreotide in CID has been purely empirical. The Canadian Working Group on CID has recommended that

No.	Author and ref.	Year	Type	Journal	Patients	Study on	Results and significance
1	Casinu S. *et al.* (22)	1993	Randomised study	J. Clin. Oncol.	41	Octreotide vs loperamide	Oct : Lop = 90.5% : 15%, $p < 0.005$
2	Gebbia V. *et al.* (23)	1993	Randomised study	Anticancer Drugs	40	Octreotide vs loperamide	Oct : Lop = 80% : 30%, $p < 0.001$
3	Barbounis V. *et al.* (24)	2001	Nonrandomised study	Support Care Cancer	13	Oct response in Drug resistant CID	response in 12 patients
4	Zidan J. *et al.* (25)	2001	Nonrandomised study	Annals of Oncology	32	Oct response in Drug resistant CID	CR in 30 cases in 3 days
5	Petrelli N.J. *et al.* (26)	1993	Nonrandomised study	Cancer	16	Oct response in Drug resistant CID	CR in 15 cases in 3-4 days
6	Cascinu S. *et al.* (27)	1992	Nonrandomised study	Eur. J. Cancer.	27	Oct response in severe CID	CR in 26 cases in 3 days

Abbreviations : Oct Octreotide
Lop Loperamide
CR Complete response
CID Chemotherapy induced diarrhoea
ref reference

Fig. 4. — Octreotide vs other drugs in CID

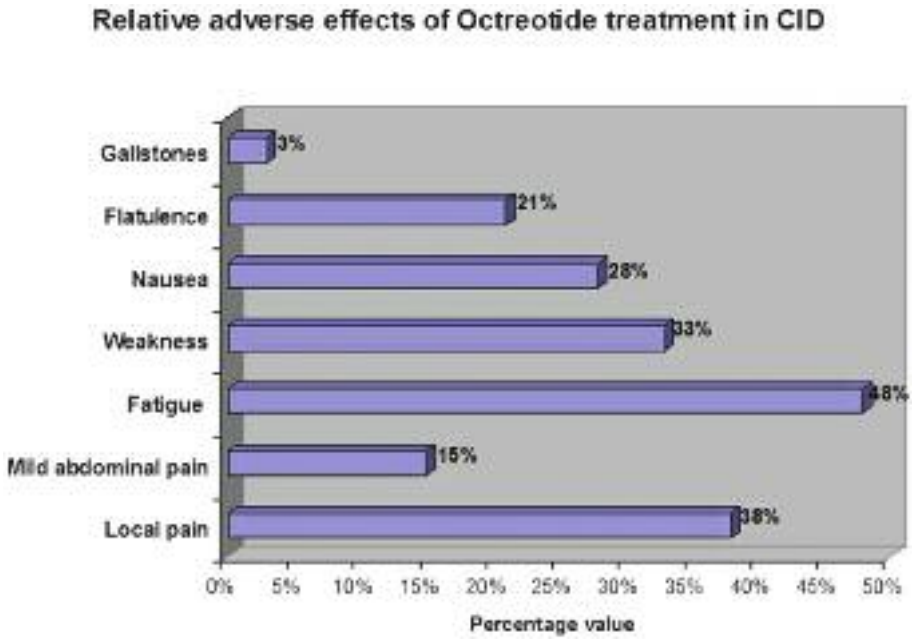

Fig. 5. — Adverse effects of octreotide in its use in chemotherapy induced diarrhoea.

patients with grade 2 CID (NCI grading) refractory to loperamide or opioids and grade 3 or 4 CID should have octreotide at a dose of 100-150 micrograms subcutaneously thrice daily. In refractory diarrhoea, doses may be increased up to 500 micrograms thrice daily (16,30). The Canadian working group also recommends that octreotide LAR 30 mg (intramuscularly, once every 28 days) can be used prophylactically in any patient with colorectal cancer receiving chemotherapy who had experienced CID with the previous cycles (16). Dose efficacy of octreotide LAR (Long acting 40 mg vs 30 mg) has been assessed by Rosenoff and colleagues in a multicentre, randomized, open-label study (31). The mean duration of anti-diarrhoeal treatment was found to be shorter for octreotide. Statistical significance was reached with both these results ($p < 0.001$). In this trial, although fewer patients in the 40 mg group experienced severe (grades 3-4) diarrhoea and unscheduled healthcare support as compared to the 30 mg group, none of these differences were statistically significant. But this trial introduced the possibility of secondary prevention of CID by octreotide. Octreotide has a positive dose-response effect in CID, as shown by Goumas *et al.* in a randomized study, where patients with severe, loperamide resisitant, CID were treated by thrice daily doses of either 100 µg or 500 µg of (subcutaneous) octreotide. Complete resolution was reported in 90.32% patients in the 500-microgram arm as compared to 60.71% in the 100-microgram arm ($p < 0.05$) (30). In a phase I trial performed to demonstrate the safe dose of octreotide in fluoropyrimidine-induced diarrhoea in 35 patients, the maximum tolerated dose was found to be 2000 micrograms (subcutaneous) thrice daily (32).

iii) *Adverse effects related to the use of octreotide in CID*

An extensive literature search has revealed that octreotide is safe, well-tolerated drug and effective with minimal adverse effects within the therapeutic range when used in CID (26,32) (Fig. 5). Local pain at the injection site was reported by Gebbia *et al.* (23) and Barbounis *et al.* (24) (incidences of 15% and 38%) in their respective studies. But none of these were severe enough for cessation of therapy. Local pain was short lived and no longer than 15 minutes. This can be avoided if the vial is warmed prior to drug administration (33). Symptoms like increased diarrhoea or looseness of stools, vitamin B12 deficiency and potential risk of gallstone formation (12-60%) are associated with long-term octreotide use in acromegaly (33,34,35), but these should not be a problem in CID, because of the short duration of therapy in the latter. However, Rosenhoff *et al.* (31) has reported an incidence of gallstones in 3% patients being treated for CID. But this study did not mention whether these patients with gallstones had ultrasound scans prior to their treatment with octreotide, and hence may be a coincidental finding. Diarrhoea or the looseness of stools in long-term treatment with octreotide is possibly because of its increase in fecal fat excretion (36). Mild abdominal pain (15%) (23) at the onset of treatment, fatigue (48%), weakness (33%), nausea (28%), flatulence (21%) and constipation (13%) are some of the other non-specific adverse effects associated with the use of octreotide in CID but none were serious enough and most of them disappeared on further treatment with octreotide (31).

Discussion

Loss of intestinal epithelium due to inflammation and superficial necrosis of the bowel wall are implicated in the pathogenesis of CID (25,29). Blocking DNA synthesis, mitotic arrest of intestinal crypt cells and increasing the relative number of immature secretory crypt cells induced by 5FU and deconjugation of the glucoronide form of SN-38 metabolite of irinotecan by intestinal bacteria are thought to be important mechanisms associated with 5FU and irinotecan-induced diarrhoea (37,38,39). Deficiency of enzymes, dihydropyrimidine dehydrogenase (DPD) and uridine diphosphate glucoronyl transferase (UGT), which are involved in the metabolism of 5FU and SN38 respectively could also make some patients prone to episodes of CID due to the toxicities of the respective agents (16,17).

i) *Octreotide and control of diarrhoea : mechanism*

Octreotide is a synthetic analogue of somatostatin, a regulatory peptide hormone with a wide range of functions. Somatostatin acts as a neurotransmitter in human central nervous system, regulates release of thyrotropin and growth hormone, affects endocrine and exocrine functions of pancreas, decreases gastrointestinal transit time and endogenous fluid secretion in jejunum (30). It inhibits secretion of hormones like vasoactive intestinal polypeptide, serotonin, gastrin, insulin, glucagons, pancreatic polypeptide and motilin. By stimulating intestinal fluid and electrolyte absorption, it increases the ratio of absorption vs secretion. This along with modulation of gastrointestinal hormone release is thought to be the mode of action of somatostatin and its analogues in controlling diarrhoea. The anti-inflammatory effects of somatostatin analogue(s) can also be responsible for its role in CID (25,30). In a research paper published by Karalis *et al.* (40), carrageenin-induced inflammation was controlled by somatostatin analogues (sandostatin and somatulin) both locally and systemically in animal models. But limitation to the pharmacological use of somatostatin is its very short half-life in human blood (t1/2 plasma = 1.1-3.0 mins) (30). Octreotide acetate is an injectible, synthetic octapeptide derivative of somatostatin and has a longer half-life of 90 minutes in the human plasma. It has been found to work for 8 hours after subcutaneous injection (24,30,31). A long acting formulation consisting of microspheres of poly-DL-lactide-co-glycoside-glucose containing octreotide has also been introduced in the market for pharmacological use. Along with having all the advantages of the short acting formulation, it has an added advantage of slow drug release, which can be effective even if used once monthly (intramuscular injection) (29). After an intramuscular injection, the serum drug levels rapidly rise to 0.03 ng/ml/mg within one hour followed by a gradual decrease to 0.01 ng/ml/mg. In 2-3 weeks from the time of injection, the drug levels gradually increase to a plateau therapeutic level and remain so for the next 2-3 weeks (41). Octreotide acetate has been used in controlling diarrhoea in carcinoid syndrome, Verner-Morrisson syndrome, graft vs host disease, AIDS related diarrhoea, radiation induced colitis, short bowel syndrome, dumping syndrome and chemotherapy induced diarrhoea (29,30). Octreotide has also been used in treating diarrhoea in patients resulting from chemo radiotherapy (42) or radiotherapy alone (43). The possibility of the use of octreotide in the secondary prevention of CID has been strengthened after the publication of the results of STOP trial (31) and few other articles (44).

ii) *Pharmacoeconomic aspects involving the use of octreotide in CID*

A study performed by Dranitsaris and colleagues looked at the financial burden of CID in terms of Canadian dollars and found that the mean expenditure for managing patients with severe (grade 3 and 4) CID was $2559 per patient, which included costs involving hospitalisation, clinic visits, laboratory and other diagnostic tests, expenditure on medical and nursing staff and supportive care. A further analysis between the cost of management of patients suffering from grade 3 and grade 4 diarrhoea demonstrated that the cost of care involving grade 4 patients was five times more ($1097 vs 5776 ; $P < 0.001$). Thus the cost incurred by the healthcare system could be significantly decreased if the patients could be prevented from developing grade 4 diarrhoea by active management (21). Similar studies are unavailable in any other healthcare settings. Studies involving comparison between care related expenses of grade 3 and 4 patients and cost of octreotide are still lacking. But from the results of the above study, the authors strongly feel that use of octreotide for every patient with grade 3 diarrhoea would contribute towards a reduction in the effective cost of care. This section is still open to further debate.

iii) *Other modes of controlling CID*

Apart from loperamide, activated charcoal and budesonide have also been used by some studies in treating CID. The incidences of all grades of diarrhoea, in a study by Michael *et al.* (45), were slightly greater in the non-charcoal treated group (79.2%) as compared to those treated with activated charcoal (53.5%). Mean number of loperamide tablets consumed by the patients who had activated charcoal was 13.1 as compared to 23.4 in the other group. But these results were statistically insignificant.

Budesonide has been found to be effective and relatively less expensive (as compared to octreotide) in treating loperamide-resistant irinotecan and 5FU induced diarrhoea (46). In a prospective, randomized, multicentre, double-blinded study performed by Karthaus M and colleagues, budesonide was used to control irinotecan-induced diarrhoea, in a cohort of patients with

advanced colorectal cancer (47). Lesser episodes and shorter duration of diarrhoea were noted in the budesonide group as compared to the placebo group. Patients receiving budesonide had a lower need for the rescue medication, loperamide for controlling diarrhoea as well. But the results of this study could not gain any statistical significance.

Conclusion

We therefore conclude that octreotide is effective in treating CID of all grades especially the ones that are resistant to other modes of treatment and has a positive impact on the patient's quality of life. Octreotide is associated with few adverse effects within the therapeutic range when used in CID and none of them are life threatening or severe enough to cause appreciable morbidity. Currently, octreotide is also being considered for prophylaxis against CID. Understandably, the cost of octreotide draws a limitation to its extensive use. The authors have cited a Canadian study, which, however, showed that the health system eventually benefitted in terms of length of hospital stay and total cost of care in Canadian Dollars when early use of octreotide prevented grade 3 diarrhoea from progressing to grade 4 disease. Further evidence possibly involving some other health systems assessing similar cost benefit ratio might be beneficial in this aspect.

With the current evidence in mind, octreotide could be considered as the drug of choice in diarrhoea of grades 3 or above resulting from chemotherapy in any colorectal cancer patient. Its use in lower grades of CID might not be cost effective and other less expensive modes of treatment like loperamide are standard.

Large randomized controlled trials comparing the roles of budesonide, activated charcoal, loperamide and octreotide would also be helpful to compare their relative effectiveness in preventing and controlling different grades of CID.

Conclusion

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