Chemotherapy-induced diarrhoea in dogs and its management with smectite

results of a monocentric open-label randomized clinical trial

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Abstract

Chemotherapy-induced diarrhea (CID) is a frequent chemotherapy adverse event in dogs. Yet, there is currently no consensus regarding its management. Smectite is a natural medical clay, widely used in the treatment of acute diarrhea in humans.

The objectives of this study were to assess the efficacy of smectite in the management of CID in dogs, and to collect epidemiological data on CID.

For each episode of diarrhea, dogs were randomized into 2 management groups: Smectite group, receiving smectite at 0.5 g/kg PO per day divided in 2-3 doses initiated at the start of CID; Control group, without initial medication. In both groups, rescue metronidazole was prescribed if CID progressed or was not improved within 48 hours.

Sixty dogs were recruited and received 426 chemotherapy administrations between June 2017 and March 2019. The incidence rate of CID was 110/426 (25.8%, 95% CI: 21.7-30.2%), and significantly differed between the chemotherapeutic drugs administered ($P < 0.001$). Metronidazole was administered in 5/54 events (9.3%, 95% CI: 3.1-20.3%) in the Smectite group and in 40/56 events (71.4%, 95% CI: 57.5-82.3%) in the Control group ($P < 0.001$). The time to resolution of diarrhea was shorter ($P < 0.001$) in the Smectite group (median: 19.5 hours, interquartile range: 13.5-32 hours) compared to the Control group (median: 53 hours, interquartile range: 31.5-113.5 hours).

The results of this study support the administration of smectite in the first-line management of CID in dogs.

Key words: antineoplastic agents, calcium aluminosilicate, diarrhea, dogs

1. INTRODUCTION

Chemotherapy-induced diarrhea (CID) is a frequent chemotherapy adverse event in dogs,[1] of which clinical severity can vary as described by the Veterinary Cooperative Oncology Group criteria for adverse events (VCOG-CTCAE) version 1.1.[2] Yet, epidemiological data is scarce since it is often reported as part of the gastrointestinal adverse events,[3,4] and the collection of more accurate information may help improve its management. In humans and rodent models, it was historically thought that CID arose solely from damage induced by chemotherapeutic agents to the rapidly proliferating cells of the basal epithelium.[5] However, alteration of the mucus layer, increased intestinal permeability, mucosal inflammation and changes in the intestinal microbiota seem to play a central role.[6-8] Various infectious agents (viral, bacterial or parasitic), and in particular *Clostridioides difficile*, may also occasionally be involved in the pathogenesis of CID in humans.[9,10] To the best of the author's knowledge, only one recent veterinary study investigated probiotics as a treatment of CID, but failed to demonstrate a potential benefit.[11] In the absence of consensus for the management of CID in dogs, it has been suggested that antibiotics such as metronidazole could be used.[12]

Although the mechanism of action of smectite is not clearly understood, it is an activated natural aluminosilicate clay that can adsorb water and presents multiple other interesting properties: it prevents toxins, bacteria and viruses adhering to intestinal membranes,[9,13-17] it has been shown to strengthen the mucosal barrier *in vitro* and *in vivo*,[18-20] to have some anti-inflammatory properties,[17,18,21,22] to decrease intestinal bacterial translocation,[23] and to stabilise the intestinal microbiome.[16,17]

Its role in the treatment of acute diarrhea in children and adults is well established,[24,25] and a beneficial effect has been found in different types of diarrhea and different species.[21,22,26-28] In a case series of 17 dogs with intractable CID, 10 dogs (58.8%) had resolution of their diarrhea after 48-72 hours of treatment, and improvement was noted in the remainder.[29]

Chemotherapy dosage is typically limited by the occurrence of adverse events, and efficient management of CID could decrease the need of dose reductions, and optimize chemotherapy dose-intensity, whilst improving the quality of life of our veterinary patients. The primary objective of this study was to assess the efficacy of smectite in the management in dogs with CID, taking the time to resolution of diarrhea as a primary outcome. A secondary objective was to collect epidemiological data on CID in dogs.

2. MATERIALS AND METHODS

2.1. Dog Selection

All dogs included in the study were presented to an academic veterinary specialty oncology service between June 2017 and March 2019. To be eligible, dogs had to meet all of the inclusion criteria: (1) to have a cytological or histopathological diagnosis of a tumor by a board-certified clinical pathologist or anatomic pathologist, respectively; (2) to receive conventional dosing regimen chemotherapy for the management of their tumor; and to meet none of the exclusion criteria: (1) to have a gastrointestinal tumor; (2) to have pre-existing diarrhea whether suspected to be related to the tumor or not. Owners were given an information sheet and were required to sign a consent form confirming that they agreed to enrol their dog in the study. Dogs were enrolled by the clinician in charge of the case, and conditions required for enrolment were verified by the first author.

2.2. Study Design

Dogs were randomized directly after enrolment, with a 1:1 allocation ratio into one of two management groups: Smectite group, or Control group. Dogs were randomized again if they developed diarrhea, so that randomization was performed for each episode of diarrhea. Some dogs may have developed several episodes of diarrhea randomized in different management groups. A randomized table was created before the study using the GraphPad QuickCalcs Web site: https://www.graphpad.com/quickcalcs/randomize1 (accessed May 2017). Diarrhea was defined as faeces with a consistency grade ≥3.5 according to the Waltham™ Faeces Scoring System (see Supplementary form 1). This study was approved by the Institutional Veterinary Ethical Review Committee, and designed to conform to the CONSORT guidelines.

2.3. Management Protocol

The smectite used in this study was in the form of hydrated calcium aluminosilicate clay with a particle size < 80 µm (VBS Rx Clay®, VBS Direct Ltd., Bulkeley, United-Kingdom). Pots contained 100g of smectite and were provided with a 500 mg measuring scoop.

Dogs in the Smectite group were provided with a pot of smectite. If they developed diarrhea, owners were instructed to give their dog smectite at 0.5 g/kg PO per day divided in 2-3 doses with food or mixed with water and syringed, starting as soon as possible. Smectite was discontinued at the time of the resolution of diarrhea, defined as 2 consecutive faeces of normal consistency (grade 2 to 3 according to the Waltham™ Faeces Scoring System); or if constipation occurred, defined as no faeces for > 24 hours or faeces with increased consistency (grade ≤ 1.5 according to the Waltham™ Faeces Scoring System). Dogs in the Control group did not receive any first-line intervention.

In both management groups, a rescue protocol was implemented to comply with the local ethical regulation. In case of progression of the diarrhea (increasing Waltham™ faeces consistency grade) or no improvement within 48 hours, metronidazole was prescribed at 10-15 mg/kg PO every 12 hours for 5 days.

Owners were asked to continue feeding their dogs with their normal routine diet during the full chemotherapy protocol; including before, during and after the development of diarrhea. This consistent recommendation was established to avoid any possible bias in the application of dietary changes. All instructions were clearly communicated to the owner by a clinician, and written on the patient discharge form provided following consultation.

2.4. Response and Toxicity Assessment

Owners were given a diary to complete in case of diarrhea, from the last normal stool to at least two non-diarrheic stools (see Supplementary form 1). They were asked to record in particular: hour of defecation, faeces consistency grade, presence of clinical signs (*e.g.* nausea, vomiting, lethargy), and drugs / supplements administered. Faeces consistency grade was recorded according to the Waltham™ Faeces Scoring System. The diary was considered inadequately filled if the faeces scoring was not continuously recorded from the start until the resolution of diarrhea, and if the doses of smectite and/or metronidazole prescribed were not all recorded. Following the collection of inadequately filled diaries, minimal information allowing the assessment of the pre-specified outcomes was collected by the first author (Q.F.), after discussion with the owners/clinicians and review of the medical records. All dogs were assessed with physical examination, full history and quality of life (QOL) questionnaire at the time of the predicted neutrophil nadir and at the time of the of following chemotherapy administration. In particular, rectal temperature was measured at each hospital visit, whether it was scheduled or not. A QOL questionnaire which had been validated by a

previous study was completed by owners at every visit as part of the routine practice in our institution, independently from this study (see supplementary form 2).[30] Predicted nadir absolute neutrophil count (ANC) were obtained from complete blood counts (CBC) performed 7 days after administration for all drugs except carboplatin, for which they were performed after 10 days. Additional CBCs were also performed when clinically indicated. Febrile neutropenia was defined as chemotherapy-induced neutropenia (ANC < 2.5 x 10^3/µL) in conjunction with fever (rectal temperature > 39.2 °C).[31] All chemotherapy-associated toxicities were recorded and graded according to the VCOG-CTCAE version 1.1.[2] Lethargy, anorexia and vomiting were used to assess constitutional/gastrointestinal adverse events. If diarrhea was thought not to be related to chemotherapy based on the history, then the event was excluded from the study.

The primary outcome was the time to resolution of diarrhea; defined as the time in hours from the first faeces with a consistency grade ≥ 3.5, to the last faeces with a consistency grade ≥ 3.5 preceding at least 2 consecutive faeces of grade ≤ 3, or to the first faeces of normal consistency if only one abnormal faeces occurred. Secondary outcomes included: prescription of rescue metronidazole, number of treatments until resolution of diarrhea, time from start of treatment until resolution of diarrhea, QOL score, hospitalization, chemotherapy-induced toxicities, alterations in chemotherapy protocol, occurrence of diarrhea at the following same drug administration.

2.5. Statistical analysis

Sample size determination was based on the hypothesis that the duration of diarrhea would be significantly shorter within the Smectite group compared to the Control group. The minimum detectable difference of the primary outcome between the two groups was set at 24 hours, with an alpha risk of 5% and a beta risk of 20%, the number of diarrhea events to be included per group was calculated to be 63. Based on our institution database, a period of about 1.5 years

was expected to collect the number of diarrhea events. An early stopping rule was established in case of reaching the scheduled closure date, because the first author (Q.F.) was no longer available to ensure the continuity of the study after this date.

Fisher's exact test was used to compare binary data, and Mann-Whitney test was used to compare ordinal and continuous non-normally distributed data. Log-rank and Wilcoxon tests were used to compare the time to resolution of the diarrhea between the two groups. The analyses were made in the intention-to-treat population.

Statistical analyses were performed by commercially available statistics software (Minitab 17 Statistical Software, State College, Pennsylvania). A P-value < 0.05 was considered statistically significant for all analyses. A 95% confidence interval (CI) was provided for the proportions. The first quartile (Q1) and third quartile (Q3) were reported to describe the interquartile range (IQR: Q1-Q3) for ordinal data. Graphs were made by commercially available graphic software (GraphPad Prism version 8.00 for Windows, La Jolla, California).

2.6. Cell line validation statement

No cell line was used in this study.

3. RESULTS

Seventy-four dogs were initially assessed for eligibility for the study. Fourteen dogs were excluded, 6 for having gastrointestinal tumors, 5 for having pre-existing diarrhea, and 3 because the owner declined to enroll their dog (Figure 1). Sixty dogs were prospectively enrolled in this study (Table 1), and 426 chemotherapy administrations were recorded (Table 2). Chemotherapy protocols included 19-week CHOP-based protocol,[32] escalating-dose vinblastine/prednisolone protocol,[33] and other single-agent lomustine, doxorubicin and

carboplatin protocols. One hundred and twelve diarrhea events were recorded, and only two were excluded because they were suspected to be secondary to general anaesthetics. Recruitment of dogs started on the 10th June 2017 and was interrupted early when the scheduled closure date was reached on the 1st April 2019, 110/126 (87.3%) of the calculated sample size was achieved.

3.1. Efficacy of smectite in the management of chemotherapy-induced diarrhea

Fifty-four diarrhea events were recorded in the Smectite group, and 56 in the Control group (Table 2). The median starting consistency grade of diarrhea events was 4.0 in both the Smectite group (IQR: 3.5-4.0) and the Control group (IQR: 3.5-4.5). Diaries were inadequately filled in 10 events within the Smectite group and in 15 events within the Control group. Smectite was not administered in 12 events recorded in the Smectite group (Figure 1). No deviation was noted with the prescription of rescue metronidazole.

In the Smectite group, the median time to resolution of diarrhea was 19.5 hours (IQR: 13.5-32 hours; Figure 2). A median of 2 doses (IQR: 1-3) of smectite was administered before resolution of diarrhea, which occurred at a median time of 18 hours (IQR: 13.5-26 hours) from starting it. Smectite administration did not result in any constipation. Metronidazole was administered in 5/54 events (9.3%, 95% CI: 3.1-20.3%). In 3 events metronidazole was administered instead of smectite (protocol deviation), which was then administered as a rescue in 1 case. In 2 events it was administered as a rescue protocol following administration of smectite. The median QOL score was 9.0 (IQR:7.0-9.0), and the median constitutional/gastrointestinal adverse event grade was 0 (IQR: 0-1). Continuous diarrhea was followed by 1 hospitalization, 1 chemotherapy discontinuation and 1 chemotherapy dose reduction.

In the Control group, the median time to resolution of diarrhea was 53 hours (IQR: 31.5-113.5 hours; Figure 2), which was significantly longer that in the Smectite group ($P < 0.001$). Metronidazole was prescribed as a rescue in 40/56 events (71.4%, 95% CI: 57.5-82.3%), which was significantly more frequent than in the Smectite group ($P < 0.001$) where it was administered in 5/54 events (9.3%, 95% CI: 3.1-20.3%). When rescue metronidazole was prescribed, a median of 6 doses (IQR: 1.75-6.25) was administered before resolution of diarrhea, which occurred at a median time of 64 hours (IQR: 46.5-99 hours) from starting it. Smectite was prescribed as a second rescue in 3 cases and was associated with resolution of diarrhea within 24 hours in 2 cases. In the 3rd case, the diarrhea continued and resolved following the administration of a probiotic. Compared to the Smectite group, there was no significant difference in the QOL score (median: 8.0, IQR:7.0-9.0; $P = 0.54$), and in constitutional/gastrointestinal adverse event grade (median: 0, IQR: 0-1; $P = 0.78$). Continuous diarrhea was followed by 4 hospitalizations, 1 chemotherapy dose delay, 3 chemotherapy dose reductions, and 2 chemotherapy discontinuations.

3.2. Epidemiology of chemotherapy-induced diarrhea

The overall incidence of diarrhea following chemotherapy administration was 110/426 (25.8%, 95% CI: 21.7-30.2%), and significantly differed between the chemotherapeutic drugs administered ($P < 0.001$). Doxorubicin and vinca-alkaloids were associated with a higher incidence, whereas cyclophosphamide was associated with a low incidence (Table 2). Only one episode of diarrhea was recorded following each carboplatin and lomustine administrations.

Diarrhea occurred from a few hours up to 13 days post chemotherapy treatment, at a median of 2 days (IQR: 1-4) following chemotherapy administration (Figure 3.a). It lasted from 4 hours to over a week with a median of 29 hours duration (IQR: 16-69.5 hours; Figure 3.b).

The median faeces consistency grade at the start and at the worst of the diarrhea were 4 (IQR: 3.5-4.5) and 4.5 (IQR: 4-5), respectively (Figure 3.c). When diarrhea occurred, it was noted again at the following administration of the same drug in 33/76 (43.4%, 95% CI: 32.0-55.2%) of instances. Based on the results of the Control group, diarrhea was rapidly self-resolving in 16/56 of instances (28.5%, 95% CI: 17.6-42.4%).

The QOL score was significantly lower when dogs developed diarrhea (median: 9.0, IQR: 7-9) compared to when they did not (median: 9.0, IQR: 8.5-10; $P < 0.001$). Hospitalization occurred significantly more frequently ($P = 0.0032$) when chemotherapy administrations were associated with diarrhea (12/110 [10.5%, 95% CI: 5.8-18.3%]) compared to when they were not (8/316 [2.5%, 95% CI: 1.1-4.9%]). Diarrhea was also significantly associated with the development of lethargy (median: 0 [IQR: 0-1] *vs.* median: 0 [IQR: 0-0]; $P = 0.0013$), anorexia (median: 0 [IQR: 0-1] *vs.* median:0 [IQR: 0-0]; $P < 0.001$), and vomiting (median: 0 [IQR: 0-1] *vs.* median: 0 [IQR: 0-0]; $P < 0.001$). Febrile neutropenia occurred significantly more frequently ($P = 0.039$) when chemotherapy administrations were associated with diarrhea (6/110 [5.5%, 95% CI: 2.0-11.5%]), compared to when they were not (5/316 [1.6%, 95% CI: 0.5-3.7%]). All cases of febrile neutropenia had concurrent anorexia and lethargy.

4. DISCUSSION

The data prospectively collected in this study provides valuable information about CID in dogs, which could be useful to further understand the development and management of this common adverse event.

Doxorubicin, vincristine and vinblastine were the drugs associated with the highest incidence of CID. Cyclophosphamide was associated with a very low incidence (4/60, 6.6%), and only 1 episode of diarrhea was reported with carboplatin (1/32, 3.1%) and lomustine (1/40, 2.5%).

Doxorubicin, vinca alkaloids and cyclophosphamide are primarily excreted within the bile and eliminated in the faeces, whilst the elimination of lomustine and carboplatin is primarily renal. It is therefore possible that it is the metabolites excreted within the intestines *via* the bile that are responsible for triggering CID. Although this has been demonstrated with irinotecan-induced diarrhea,[34] the mechanisms of anthracyclines- and vinca alkaloids-induced diarrhea remain largely unexplored and further investigations are needed.

Since less than half of the dogs will have another episode of CID at the following drug administration, the implementation of prophylactic measures and especially chemotherapy dose reductions is of questionable value. Prophylactic actions could be discussed on an individual basis, if CID develops following two consecutive administrations, or if the event of CID is severe enough to require hospitalization. Smectite has been used prophylactically successfully in horses to prevent post-operative diarrhea, and prophylaxis with smectite would need to be further investigated in dogs.

In the current study, CID was significantly associated with a lower QOL score, with a higher incidence of hospitalization, and higher grade of lethargy, anorexia, vomiting and febrile neutropenia toxicities. No significant difference between the Smectite and the Control group was noted in the intention-to-treat analysis, but a causal relationship remains possible and could be further explored with an appropriately powered multicentric study.

This study was designed to compare the resolution of CID following the administration of smectite compared to no intervention since there is currently no consensus recommendation regarding the management of CID in dogs.[12] However, for ethical concerns, an identical rescue protocol with the administration of metronidazole was applied in both study groups. Metronidazole was chosen because its use has already been suggested for the management of CID in dogs,[12] and to comply with the local ethical regulation as it was already in our

standards. Nonetheless, metronidazole in dogs significantly reduces bacterial diversity indices, alters the microbiome composition and may increase the risk of occurrence of nosocomial or opportunistic infections with microbial resistance.[35] Chemotherapy is also associated with significant alterations in the microbiome and a dramatic decrease in anaerobes in particular, which may contribute to CID.[36-38] Both metronidazole and chemotherapy affect *Clostridium* cluster *IV* and *XIVa*, which are known to positively affect the gut health through improved nutrient absorption, production of short chain fatty acids with anti-inflammatory properties, and epithelial maturation.[35,36] Antibiotic usage in human chemotherapy patients is associated with colonization of pathogenic diarrhea, *Clostridioides difficile* being an increasing concern.[9,38,39] Antibiotics may also be associated with a poorer outcome in human cancer patients, possibly in part due to decreased chemotherapy and immunotherapy efficacy.[40-42] The administration of antibiotics in human cancer patients with CID is reserved for those at higher risk of septic complications (e.g. fluoroquinolone) and for the prevention of irinotecan-induced diarrhea (e.g. neomycin).[43] For these reasons, the systematic administration of metronidazole from the start of diarrhea as a first-line treatment cannot be recommended, especially when 28.5% of CID is rapidly self-resolving.

Smectite was investigated in this study as it is commonly used to manage acute diarrhea in both pets and humans. Administration of smectite in dogs at a dosage of 0.5 g (total dose per dog) given orally every 6 hours has been suggested and reported to be successful in the management of acute diarrhea.[29,44] However, the dosage chosen for this study (*i.e.* 0.5 g/kg per day divided in 2-3 doses) was higher for several reasons: (1) based on personal experience and the summary of product characteristics from another manufacturer of smectite (Smectivet®, Boehringer Ingelheim, Reims, France); (2) resolution of CID as quickly as possible may be more important than in other situations since a decreased QOL in canine cancer patients may result in alterations in chemotherapy protocols, and the interval between

drug administrations may be short especially in multidrug protocols; (3) properties of smectite are dose-dependent;[21] (4) higher dosages of 0.6 g/kg per day and 1 g/kg per day have been used successfully in rats and horses, respectively;[23,28] whilst the use of a lower dosage for CID in humans did not seem efficient in the management of CID.[45]

Administration of smectite at 1 g given orally every 6 hours for the prevention of irinotecan-induced diarrhea in humans was indeed considered ineffective, although there was significantly more patient drop-out in the placebo arm.[45] Diosmectite was however remarkably effective in the treatment of chemotherapy-induced oral mucositis in humans,[46] which is reported to have similar pathophysiologic mechanisms as gastro-intestinal mucositis.[5] In this study, 85.7% of patients treated with a diosmectite cream obtained complete regression of oral mucositis after 5 days of treatment, compared to only 3% for the controlled group.[46] It is possible that the topical oral administration resulted in a higher mucosal concentration of smectite, necessary to efficiently treat mucositis. It is also possible that smectite is less effective at preventing mucositis than treating it. Further studies investigating other dosing regimen are warranted before concluding that smectite truly is ineffective in the management of CID in humans.

The results of this study support the administration of smectite as first-line management of CID in dogs. A multicentric randomized clinical trial should ideally be performed to confirm this finding. An adaptive increasing dosage should be explored, as this may further increase its efficacy. The benefit of metronidazole as a rescue remains unclear, and with a median time of 64 hours of administration until resolution of diarrhea, alternative rescue protocols should be explored. Some dogs have recurrent episodes of diarrhea and may benefit from prophylactic measures. Low-dose smectite and/or probiotics should also be investigated in this context.

This study had several limitations. It was non-blinded and the results are therefore subject to bias. However, we believe the strong differences in several outcomes including the time to resolution of diarrhea support the relevance of the findings. Also, no deviation in the prescription of rescue metronidazole was noted, the deviations in completing the diaries were similar in both groups, and owners completed the QOL questionnaires as part of the routine practice in our institution. The second limitation was the early interruption of the trial, increasing the risk of a type I error when analysing the primary outcome. This risk is however minimal since the trial was stopped late in its course achieving nearly 90% of the predetermined sample size after 21 months, and a type I error is considered very unlikely with a *P*-value < 0.0005,[47] which was our case. Furthermore, the risk of introducing a bias is considered low when a study is stopped independently from the result.[48] The third limitation was the presence of protocol deviations, which may have ultimately affected the results of this study by decreasing or masking the difference in the primary and secondary outcomes between the two groups. A fourth limitation is that dogs were maintained on their routine diet during diarrhea. Diet composition may affect the intestinal microbiome and therefore dogs may have responded differently to the management of their diarrhea depending on their routine diet.[49,50]

5. CONCLUSION

The administration of smectite at 0.5 g/kg PO per day divided in 2-3 doses was associated with a significantly reduced time to resolution of diarrhea and decreased prescription of rescue metronidazole. The results of this study support the administration of smectite in the first-line management of CID diarrhea in dogs. These results should also encourage further

investigations of the potential benefit of smectite for the management of other types of diarrhea in dogs, and for the management of CID in humans.

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TABLES

TABLE 1 Characteristics of the 60 dogs included in the study.

Parameter	
Age (years)	
Median (range)	9.0 (4.0-16.2)
Sex	
Male	37
Female	23
Weight (kg)	
Median (range)	25.2 (4.5-62.5)
Breed	
Labrador Retriever	12
Cocker Spaniel	5
Border Collie	4
Golden Retriever	3
Scottish Terrier	3
Crossbreed	9
Other breeds (≤ 2)	24
Tumor type	
Lymphoma	30
Mast cell tumor	9
Hemangiosarcoma	6
Other sarcomas	6
Histiocytic sarcoma	4
Carcinomas	3
Melanomas	2

459 **TABLE 2** Incidence of diarrhea among the 426 chemotherapy administrations included in the

460 study

Drug	Administration	Overall incidence of diarrhea		Overall incidence rate of diarrhea
		Control group	Smectite group	
Vincristine	120	37		30.8% (95% CI: 22.7-39.9%)
		22	15	
Doxorubicin	90	37		41.1% (95% CI: 30.8-51.9%)
		19	18	
Vinblastine	75	25		33.3% (95% CI: 22.8-45.1%)
		8	17	
Cyclophosphamide	60	4		6.6% (95% CI: 1.8-16.1%)
		3	1	
Lomustine	40	1		2.5% (95% CI: .06-13.1%)
		1	0	
Carboplatin	32	1		3.1% (95% CI: .07-16.2%)
		1	0	
Epirubicin	7	5		*
		2	3	
Mitoxantrone	2	0		*
Total	426	110		25.8% (95% CI: 21.7-30.2%)
		56	54	

461 * Incidence rate not calculated because of low number of drug administrations

462 CI, confidence interval.

463 The difference in the incidence rate of chemotherapy-induced diarrhea among drugs was significant by

464 Pearson's chi squared test ($P < 0.001$).

FIGURES

FIGURE 1 Flow diagram of the study

FIGURE 2. Kaplan-Meier analysis of time to resolution of diarrhea

The median time to resolution of diarrhea was 19.5 hours (IQR: 13.5-32 hours) in the Smectite group and the 53 hours (IQR: 31.3-113.5 hours) in the Control group. The difference was significant by Log-rank and Wilcoxon tests ($P < 0.001$ for each). IQR, interquartile range.

FIGURE 3.a Time of occurrence of chemotherapy-induced diarrhea

Chemotherapy-induced diarrhea occurred from a few hours up to 13 days post chemotherapy treatment, at a median of 2 days (IQR: 1-4) following chemotherapy administration. IQR, interquartile range.

FIGURE 3.b Duration of chemotherapy-induced diarrhea

Chemotherapy-induced diarrhea lasted from 4 hours to over a week with a median of 29 hours duration (IQR: 16-69.5 hours). IQR, interquartile range.

FIGURE 3.c Starting and worst faeces consistency grade of chemotherapy-induced diarrhea

The median faeces consistency grade at the start and at the worst of the diarrhea were 4 (IQR: 3.5-4.5) and 4.5 (IQR: 4-5), respectively. IQR, interquartile range.