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Short Communication

Challenges and Pitfalls When Measuring Malabsorption in Hospitalized Patients with Haematologic Malignancies

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Abstract

Background & Aims: High dose chemotherapy- or graft versus host disease-induced gastro-intestinal mucositis occurs in 90% of the patients undergoing allogeneic HCT, with watery diarrhea as one of the key symptoms. Several methods are available to objectify and quantify malabsorption or impaired intestinal function, but not validated in patients with haematological malignancies. We set up a study to investigate whether these gold standard methods are valid markers for detecting malabsorption and applicable in clinical practice. Unfortunately, it appeared unfeasible in this patient group. This manuscript therefore addresses the challenges and pitfalls of this observational study. **Methods:** The study had a cross sectional and observational study design, aiming to include 45 adult patients with hematological malignancies with chemotherapy- or GVHD-induced-mucositis and severe diarrhea. To assess intestinal function and quantify malabsorption, patients undergo a citrulline generation test and 72-hour collection of feces in pre-weighted bucket combined with 96-hour actual registration and calculation of nutritional intake. **Results:** During 21 months study period 12/71 (17%) of patients who fulfilled inclusion, criteria were included, of which 10 of them were male and all participants had chemotherapy-induced-mucositis. Main reason for not participating was patients feeling too ill to collect feces. Only 3 patients were tested according to the research protocol. **Conclusion:** Measuring intestinal function using gold standard is unfeasible in practice in this patient group. It is important to be aware that, although firm conclusions cannot be drawn, severe treatment-related diarrhea may be accompanied by malabsorption and this should be allocated in treatment protocols so that risks in nutritional- and/or hydration status can be monitored and anticipated if necessary.

Keywords: Malabsorption; Haematological Malignancies; Citrulline; Bomb Calorimetry

Introduction

In the Netherlands, approximately 10.000 patients are annually diagnosed with haematological malignancies ranking it the number 5 most common form of cancer in women and men [1]. A subset of these patients receives an allogeneic haematopoietic cell transplantation (HCT) as consolidation therapy. Gastrointestinal mucositis occurs in 90% of the patients undergoing allogeneic HCT [2,3], as a result of high dose chemotherapy or as a consequence of graft versus host disease (GVHD) of the digestive tract. Watery diarrhea is one of the key symptoms of mucositis, causing malabsorption of nutrients, electrolytes and fluid. This poses patients at risk for malnutrition. Several methods are available to objectify and quantify malabsorption or impaired intestinal function. Fecal volume, fecal energy and macronutrient content (by bomb calorimetry or near infrared spectroscopy (NIRs)) combined with accurate assessment of nutrient intake and fasting serum citrulline or citrulline generation test (CGT) are intensively studied and implemented as tools to quantify malabsorption [4,5] in high risk patients such as patients admitted at intensive care unit (ICU), patients with short bowel syndrome, refractory celiac disease or chronic GvHD of the digestive tract [6-9].

Recently we proposed the possible role of citrulline as biomarker in patients with GVHD or chemotherapy induced mucositis [10]. We set up a study to objectify the incidence of malabsorption and quantify the degree of malabsorption in patients with haematological malignancies high dose chemotherapy- or GVHD-induced-mucositis during hospitalization. We investigated whether fecal volume, bomb calorimetry and fasting serum citrulline or CGT are valid markers for detecting malabsorption, and investigated their applicability in clinical practice. Unfortunately it appeared unfeasible to perform these gold standard methods in this patient group. This manuscript therefore addresses the challenges and pitfalls of this observational study.

Material, patients & methods

The study had a cross sectional and observational study design, aiming to include 45 adult patients with haematological malignancies admitted to the clinical haematology ward of Amsterdam University Medical Centers (Amsterdam UMC) for chemotherapy or allogeneic HCT. Inclusion criteria were haematological malignancy with chemotherapy- or GVHD-induced-mucositis and severe diarrhea. Baseline and clinical data were collected on type of malignancy, therapy, anthropometrics, laboratory parameters (thrombocytes, leucocytes, albumin, eGFR, creatinine, urea, magnesium, phosphate, sodium, potassium, serum glucose, bilirubin, alkaline phosphatase, ALAT), and nutritional support (oral, enteral or intravenous) during hospital admission. To assess intestinal function and quantify malabsorption, patients were asked to undergo 2 tests: a CGT after an overnight fast according to prescribed procedures [5], and 72 hour collection of feces in pre-weighted bucket combined with 96 hour actual registration and calculation of nutritional intake. The results of these measurements were then used to calculate the intestinal absorption capacity (i.e. energy and nutrient feces loss expressed as % of intake [4])). Feces collection was done by nurses. They also performed the CGT which involved collecting blood before and 75 and 90 minutes after ingestion of a fixed dose of glutamine (100 ml Dipeptiven®, containing 20 g alanylglutamine).

The study was approved by the Medical Ethical Committee of Amsterdam UMC, and written informed consent was obtained from the participants.

Results

Figure 1 displays the flowchart showing that in the 21 months study period (January ‘22-September ‘23) only 12/71 (17%) of eligible patients who fulfilled the inclusion criteria were included. The main reason for not participating was patients feeling too ill to collect feces. Ten male and 2 female patients, aged 57.8 ± 11.7 year were included. Two patients dropped out after inclusion. Study participants were diagnosed with acute myeloid leukemia (AML, n=8), primary myelofibrosis (n=1), and myelodysplastic syndrome (MDS)/Myeloproliferative neoplasia (MPN, n=1). Eleven patients had received an allogeneic HCT (all from an unrelated HLA-identical donor) and 1 patient had received an autologous HCT. All participants had chemotherapy-induced-mucositis, with a mean grade of mucositis of 1±0.89 [11]. Of these 10 final patients, 7 patients were able to collect feces, of whom only 3 fulfilled the feces collection according to procedures (72 hour). In 8 patients the CGT was performed. Only 3 patients were tested according to the research protocol (feces collection and CGT). (Supplementary Tables 1 and 2) depict data and characteristics of study participants.

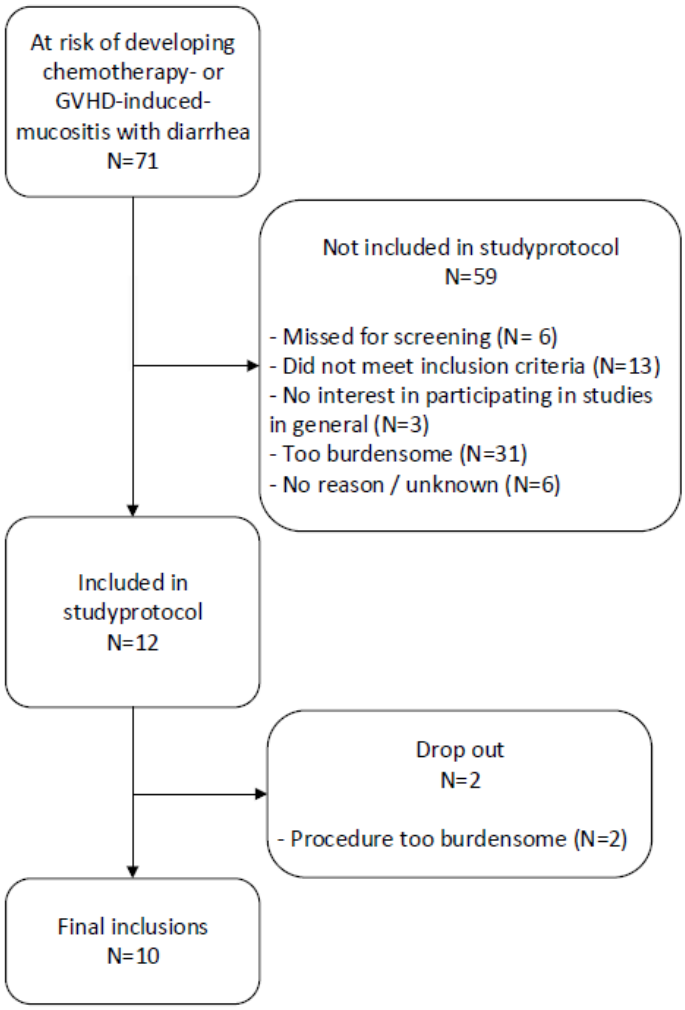

Figure 1: Flowchart.

Discussion

Despite careful consideration of the chosen methods to diagnose malabsorption or impaired intestinal function and despite the extensive experience with it within our research team, it appeared unfeasible to include sufficient numbers of patients and perform the tests as planned. Although it was known that the tests were cumbersome, it formerly appeared feasible in critical ill patients at the ICU [6,9], and in other groups of patients with severe diarrhea and malabsorption such as short bowel syndrome, autoimmune enteropathy [8], and non-hospitalized patients with GvHD [7].

The finding that most patients eligible to participate could not be included strengthens the notion that these patients are severely ill and weakened. In fact, the weakness of these patients may well be related to malabsorption. Despite the fact that patients admitted to the ICU tend to be more severely ill, a feces collector can be used and makes it easier to collect feces in these patients. Because of thrombopenia in patients with hematological malignancies, a feces collector is not used in this patient group. With the patients that did participate, there might possible be inclusion bias, since only 1 patient required total parental nutrition. But even then we measured indeed diarrhea (with high fecal water content/low dry matter content) in the 7 included patients and a low (mean) fasting serum citrulline in the 8 patients (11±7 µmol/L versus normal value of >30 µmol/L) indicating intestinal dysfunction [12].

Even though our data on intestinal (dys) function are insufficient to draw any firm conclusions, we considered it important to share our experience as it expands our knowledge and helps other researchers avoid wasting time and funds on unproductive avenues. Also 'negative' results and formats are valuable to describe and share [13]. Taken together, intestinal function, nutritional status and method of nutrition administration are relevant topics in the treatment of patients with hematological malignancies and severe treatment-related diarrhea. Despite the fact that measuring intestinal function using the gold standard is unfeasible in practice in this patient group, it is important to become aware that severe treatment-related diarrhea may be accompanied by malabsorption. The degree of diarrhea should therefore be allocated in treatment protocols so that risks in nutritional- and/or hydration status can be monitored and can be anticipated if necessary.

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11. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, November 2017, National Institutes of Health, National

Supplementary table 1: Patient characteristics (N=10)

Age (y)	65.7 ± 2.5
Gender n (%)	9 male (90%), 1 female (10%)
Body weight (kg)	83.9 ± 9.7
Height (cm)	184.6 ± 4.1
Body Mass Index (kg/m^2)	24.6 ± 2.6
Nutritional intake (N=7)*×	
Energy (kcal/d)	1593 ± 646
Fat (g/d)	56 ± 30
Carbohydrates (g/d)	200 ± 81
Protein (g/d)	60 ± 23
Alcohol (g/d)	0 ± 0
Fecal analysis (N=7)*×	
Volume (g/d)	364 ± 254
Energy (kcal/d)	178 ± 129
Fat (g/d)	10.8 ± 11.1
Protein (g/d)	9.9 ± 4.9
Remaining energy (kcal/d)	32 ± 32
Dry weight (%)	12.0 ± 4.8
Intestinal absorption capacity (%) (N=7)*×	
Energy	88.9 ± 6.5
Fat	82.6 ± 22.6
Protein	83.1 ± 7.0
Remaining energy	93.8 ± 4.8

Citrulline Generation Test (CGT) (N= 8)▫×	
Baseline fasting serum Cit (µmol/L)	11.1 ± 7.6
75 minutes after oral intake of Dipeptiven (µmol /L)	16.5 ± 10.0
90 minutes after oral intake of Dipeptiven (µmol /L)	15.9 ± 9.9

*2 patients only had data on fecal analysis, in 2 patients fecal analysis is not fully implemented in accordance with protocol, ×3 patients have complete date on fecal analysis and CGT, ▫ 3 patients only had data on CGT

Supplementary table 2: Study parameters

Participant	Gender (m/f)*	Feces analysis	Citrulline Generation Test (CGT)	Dietary intake reporter (d)	Type of haematological malignancy	Length of admission	Applied nutritional therapy (EN or PN)×
1▫	m	✓ +/- 50%	✗	4	AML	30	None
2#	m	✓	✓	4	AML	28	None
3#	m	✓	✓	4	AML	41	None
4▫	m	✓ 38 hours	✗	1	AML	50	PN 1950 ml Olimel N9E
5+	m	✓ 24 hours	✓	1.5	AML	30	None
6◊	m	✗	✓	-	Primairy myelofibrosis	44	None
7#	m	✓	✓	4	AML	46	None
8+	m	✓ 24 hours	✓	1	AML	22	None
9◊	m	✗	✓	-	MDS/MPN overlap	31	None
10◊	f	✗	✓	-	AML	24	None

*m=male, f= female; ×during period of fecal collection and output of CGT; ▫ = only fecal analysis; ◊ = only CGT; + = fecal analysis and/or CGT not fully implemented in accordance with protocol; # = complete data of fecal analysis and CGT