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ORIGINAL ARTICLE

Assessment of diarrhea as side effect of oral targeted antineoplastic agents in clinical practice

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Abstract

Background Diarrhea is one of the most frequent class adverse events associated with targeted oral antineoplastic agents (OAAs). Our objective was to analyze the incidence, characteristics, and severity of diarrhea in cancer patients in clinical practice.

Methods An observational, longitudinal, and prospective study of cancer outpatients treated with targeted OAAs was carried out in a tertiary hospital. Targed OAAs analyzed were anaplastic lymphoma kinase inhibitors, BCR-ABL inhibitors, cyclin-dependent kinase inhibitors, epidermal growth factor receptor inhibitors, mTOR inhibitors, poly (ADP-ribose) polymerase inhibitors, and vascular endothelial growth factor receptor inhibitors. Patients were given a data collection form to record daily the number, severity (CTCAE version 5.0), and characteristics of stools during the first 30 days of treatment with OAAs. Multivariate analysis was performed to identify risk factors associated with the incidence of diarrhea.

Results We analyzed 240 patients, of whom 28.7% experienced diarrhea (25.4% grades 1–2 and 3.3% grades 3–4). Patients treated with EGFR and VEGFR inhibitors had a higher incidence of diarrhea. The multivariate analysis revealed that taking the OAA with food was associated with a lower risk of diarrhea (OR = 0.404 [0.205–0.956], $p = 0.038$).

Conclusions More than a third of patients in treatment with OAAs presented diarrhea (any grade), and 22.1% of stools were semi-liquid/liquid. In multivariate analysis, taking the OAA on an empty stomach was associated with a statistically significant increase in the incidence of diarrhea.

Keywords Diarrhea · Oral antineoplastic agent · Safety · Side effect · Toxicity

Introduction

The development of targeted oral agents to treat cancer has intensified in recent years, and these medications now account for 40% of all antineoplastic drugs [1]. Targeted oral antineoplastic agents (OAAs) have become an essential part of the treatment armamentarium in several types of tumors [1]. Overall, their action mechanisms consist of blocking specific aspects of cell or tumor biology, such as the inhibition of protein kinases as a therapeutic target. These drugs lead to significant improvement in survival rates. To achieve this efficacy, it is very important to manage toxicity appropriately. Although targeted OAAs are generally better tolerated than traditional chemotherapy, their toxicity must be closely monitored, since it could be a cause of treatment withdrawal. OAAs can present different adverse events, especially skin and gastrointestinal toxicities [2]. Diarrhea is one of the most limiting adverse events of these drugs.

The mechanisms responsible for diarrhea associated with OAAs are not fully understood, although they are likely multifactorial, involving dysregulated ion transport, inflammation, and mucosal injury [3]. OAAs can directly damage the gastrointestinal mucosa, in turn causing inflammation, edema, ulceration, and atrophy and producing excessive secretion of

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fluids in the intestinal lumen [4, 5]. Excess chloride secretion during treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) is thought to cause secretory diarrhea. The severity of diarrhea is dose-dependent and can be modulated by decreasing the total dose [6]. Thus, onset is often followed by dose reduction or even discontinuation of treatment. Diarrhea affects quality of life and is associated with decreased adherence, which eventually worsens clinical outcomes [2, 7].

Accurate grading of the severity of diarrhea is very important for initial management and for subsequent changes in patients' anticancer treatment [8]. Severity of diarrhea is assessed in clinical trials using the Common Toxicity Criteria for Adverse Events (CTCAE) classification [9]. However, this does not consider factors such as the onset and duration of diarrhea or other associated signs. Several authors recommend evaluating the severity of diarrhea according to stool frequency and consistency, the presence of nocturnal diarrhea, and the presence of steatorrhea and/or blood in stool [6, 8, 10, 11]. For instance, guidance from the UK on the management of gastrointestinal side effects of cancer therapies emphasizes three crucial factors as follows: whether there is steatorrhea; whether there is fecal urgency or incontinence; and whether the patient wakes from sleep to defecate [6]. However, very few studies analyze the characteristics of these stools in clinical practice. Such an analysis would improve management and reduce complications. Since most studies focus on the use of fluoropyrimidines [3, 12, 13], evidence on diarrhea associated with targeted OAAs is very limited, with the exception of neratinib, a drug able to induce diarrhea in more than 90% of patients, what has promted the conduct of some trials with antidiarrheic drugs [14].

Our study aimed to analyze the incidence, characteristics, and severity of diarrhea in cancer patients in a real-world setting during the first 30 days after starting treatment with targeted OAAs. Our secondary objective was to identify risk factors related to the occurrence of diarrhea in these patients.

Methods

Study design and setting

We performed an observational, longitudinal, and prospective study of cancer outpatients treated with targeted OAAs in a tertiary hospital. Patients included were followed up prospectively for the first 30 days after the start of treatment with the targeted OAA. The study was approved by the local ethics committee and conducted in accordance with the ethical principles of the Declaration of Helsinki. Patients signed an informed consent before entering the study.

Patients

The study population comprised consecutive adult outpatients diagnosed with solid tumors who started treatment with a targeted OAA between 2015 and 2019. We excluded various types of patients, as follows: patients who had received a targeted OAA as part of a clinical trial; patients who started treatment with a targeted OAA while hospitalized; patients with colostomy, gastrectomy, diverticulitis, inflammatory bowel disease, chronic diarrheal syndromes, or short bowel syndrome; and patients with difficulty understanding and/or filling out the data collection form (DCF).

The sample size was calculated taken into account the incidence of diarrhea reported in the OAA summary of product characteristics. We considered that a sample size of 300 sufficed to estimate with a 90% confidence and a precision ± 5%, a population percentage considered to be around 40% of diarrhea incidence. It was anticipated a replacement rate of 15%. We considered all the cancer outpatient who met the inclusion criteria.

Data recorded and variables

Baseline data were collected from both the electronic health record and the clinical interview with the oncology pharmacist before starting treatment with an OAA dispensed at the Hospital Outpatient Pharmacy. The variables recorded at the onset of treatment were as follows:

- Demographic data: date of birth and gender.
- Clinical data: type of tumor, Eastern Cooperative Oncology Group (ECOG) performance status [*ECOG 0*: fully active, able to carry on all pre-disease performance without restriction; *ECOG 1*: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; *ECOG 2*: ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours; *ECOG 3*: capable of only limited self-care; confined to bed or chair more than 50% of waking hours; *ECOG 4*: completely disabled; cannot carry on any self-care; totally confined to bed or chair], celiac disease, lactose intolerance, and abdominal surgeries or radiation therapy to the abdomen or pelvis in the previous year. We also recorded the basal mean number of stools per day, their consistency (solid or semi-liquid/liquid), and the presence of blood before starting treatment with the OAA.
- Pharmacotherapeutic data: type of targeted OAAs and dose. OAAs were classified as follows: anaplastic lymphoma kinase (ALK) inhibitors, BCR-ABL inhibitors, cyclin-dependent kinase (CDK) inhibitors, EGFR inhibitors, mTOR inhibitors, poly (ADP-ribose) polymerase

inhibitors (iPARP), vascular endothelial growth factor receptor (VEGFR) inhibitors, and others.

At the time of dispensing the OAA, a DCF was given to the patient for daily recording of the number and characteristics of stools and the consumption of antidiarrheal drugs in case of diarrhea during the first 30 days of treatment. This DCF had a different sheet for each day. The patient recorded the following variables:

- Clinical variables: fever, vomiting, visits to the emergency room, and significant changes in eating habits during the follow-up period.
- Stool-related variables: time of the stool and its characteristics (consistency [solid or semi-liquid/liquid], presence of steatorrhea and/or blood in the stool, pain associated with the stool, and fecal incontinence). Severity was classified according to the National Cancer Institute CTCAE, version 5.0 [9] based on the increase in the number of stools per day compared with baseline.
- Pharmacotherapeutic variables: day time administration of the targeted OAA and the time between the administration and intake of meals. Need for antidiarrheal drugs (type, dose, and day time administration) and the number of concomitant medicines (including over-the-counter drugs and herbal products) taken during this period.

Statistical analysis

Data were only analyzed for patients who adequately completed the DCF; otherwise, patients were considered lost to follow-up, since they were invaluable for the study purpose.

The characteristics of patients and diarrhea were described using the mean value (SD) for continuous data and frequencies for categorical variables. The Kolmogorov-Smirnov test was used to study the normality of the numerical variables, and thus, it was possible to use the most appropriate statistical test for each variable. Continuous variables were compared using the *t* test when the distribution was normal or the Mann-Whitney test when it was not. Categorical variables were compared using an uncorrected chi-square test or Fisher exact test.

The relationship between numerical variables was examined using the Pearson correlation coefficient. In case the variables were ordinal, we used the Spearman rho test. Multivariate binary logistic regression analysis was performed to identify risk factors associated with the occurrence of diarrhea. The dependent variable was the presence of diarrhea. Exploratory variables were sex, age, ECOG, type of tumor, type of OAA, and taking the OAA with food or on an empty stomach. For this model, we used baseline data. Data were analyzed using IBM SPSS Statistics for Windows, Version 21.0. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics

A total of 304 patients signed the informed consent to participate in the study. Sixty-four patients were lost to follow-up and considered invaluable (Fig. 1).

The final study population comprised 240 patients (65.0% male) with a mean (SD) age of 61.8 years (13.2). Performance status was as follows: ECOG = 0, 67.5%; ECOG = 1, 31.2%; and ECOG = 2, 1.3%. The most frequent types of tumors were breast cancer ($n = 68$; 28.3%), renal carcinoma ($n = 58$; 24.2%), non-small cell lung cancer ($n = 44$; 18.3%), gastrointestinal stromal tumor ($n = 22$; 9.2%), and sarcoma ($n = 18$; 7.5%). During the last year, 5.4% of patients had undergone abdominal surgery and 3.3% had received abdominal and/or pelvic radiotherapy. In addition, 3.3% were intolerant to lactose and 1.3% had celiac disease. Sixteen patients (6.7%) reported that they modified their diet at the beginning of treatment with OAAs.

We assessed 27 different targeted OAAs. The number of concomitant medicines per patient was 3.7 (3.0). A total of 208 patients (86.7%) started treatment with a full dose of OAA according to the summary of product characteristics (SPC). OAAs were administered on an empty stomach in 32.1% of cases. Most of the patients (98.8%) complied with the recommendations for administration on an empty stomach as defined in the SPC.

Characteristics of diarrhea

Stool characteristics

The baseline mean (SD) number of stools per patient before starting the treatment with the targeted OAA was 1.2 (0.7). In 10.8% of patients, the baseline stools were semi-liquid/liquid, and blood was present in 1.7%. The number of stools was significantly altered in 37.9% of patients (28.7% had diarrhea and 9.2% had constipation). The mean (SD) number of stools during the first 30 days of treatment was 1.5 (0.7). Of note, 22.1% were semi-liquid/liquid, and 3.3% were associated with pain. Blood was observed in 1.2% and steatorrhea in 1.5%. In addition, 2.8% were associated with fecal incontinence.

Diarrhea incidence

A total of 69 (28.7%) patients had diarrhea during the first 30 days of treatment with OAA. The incidence of diarrhea

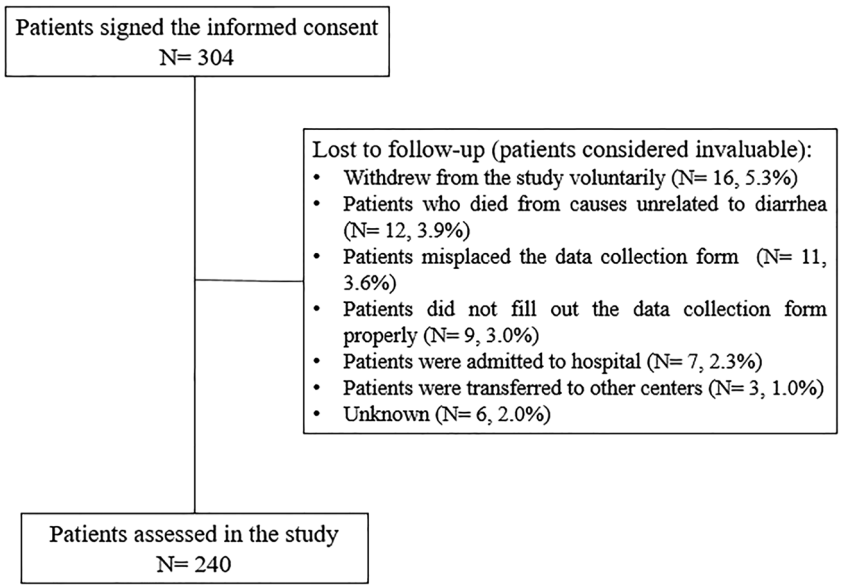

Fig. 1 Description of the recruitment of the study patients

by OAA was as follows: EGFR inhibitors, 44.8%; VEGFR inhibitors, 35.9%; BCR-ALB inhibitors, 33.3%; ALK inhibitors, 20%; CKD inhibitors, 14.6%; mTOR inhibitors, 14.6%; and iPARPs, 10%. Table 1 describes the incidence of diarrhea for each of the OAAs.

Diarrhea severity

The maximum severity of diarrhea was grade 1 in 13.7% of patients, grade 2 in 11.7%, grade 3 in 2.9%, and grade 4 in 0.4%. Table 2 compares the main characteristics of patients according to severity of diarrhea. At least 1 episode of nocturnal diarrhea was recorded in 33.3% of patients during the follow-up period. Thirty-nine patients (16.3%) took antidiarrheal drugs (loperamide in all cases), with a mean treatment duration of 6.9 days (SD 7.4) per patient. Almost half of the antidiarrheal drugs (48.7%) were administered 1–3 days after initiation of the OAA.

Correlation between diarrhea and other variables

Statistically significant differences were found in the number of stools at different times during the day ($r = 0.114$, $p < 0.001$), with a higher number of stools from 08.00 am to 11:59 am (Fig. 2). No statistically significant differences were found in the number of stools over the 30-day follow-up ($r = 0.021$, $p = 0.080$). Men had more stools per day than women (1.6 [SD 0.7] vs. 1.4 [SD 0.6], $p = 0.027$, respectively). The mean number of stools per day was lower when the OAA was taken with food (1.3 [SD 0.9] stools per day) than when taken on an empty stomach (1.6 [SD 1.1], $p = 0.002$). The correlation between the number of stools per day and the other variables are shown in Table 3.

All patients were included in a binary logistic regression analysis (Table 4). After adjustment for confounders, taking the OAA with food was associated with a lower risk of diarrhea.

Discussion

Our study analyze the incidence, progress, and characteristics of diarrhea, as well as the risk factors for diarrhea, in a large number of patients taking targeted OAAs. Most published studies in clinical practice focus only on the incidence and maximum severity of diarrhea [2, 4, 6, 15]. Besides, there is very little evidence on new targeted OAAs administered under conditions of clinical practice with respect to diarrhea characteristics. In our study, a total of 240 patients treated with targeted OAAs were followed up for 1 month. Among our results, we highlight that taking the OAA on an empty stomach was associated with an increased risk of developing diarrhea. We also observed a change in the incidence of stool episodes after initiation of the OAA in 37.9% of our patients; this took the form of an increase in 28.7%. Not only did their incidence increase, but their consistency also varied. Before starting treatment, only 10.8% of stools were semi-liquid/liquid, whereas during treatment, this value rose to 22.1%. However, steatorrhea, blood in stool, and fecal incontinence were uncommon in the present study, and these findings were not associated with other patient or drug-related characteristics.

Concerning the progress over time, we found no statistically significant differences in the number of stools over the first 30 days, although we did observe that diarrhea was more frequent during the morning. Typically, diarrhea induced by oral anticancer drugs is more frequent and intenses within the

Table 1 Incidence of diarrhea of targeted oral antineoplastic agents assessed in the study

Type of targeted oral antineoplastic agent (total no. of patients; %)	Drug (total no. of patients; %)	Diarrhea incidence (no. of patients; %)
ALK inhibitors (n=10; 4.2%)	Crizotinib (n=6; 2.5%)	2; 33.3%
	Alectinib (n=4; 1.7%)	0; 0%
BCR-ALB inhibitors (n=15; 6.3%)	Imatinib (n=15; 6.3%)	5; 33.3%
CDK inhibitors (n=30; 12.5%)	Palbociclib (n=21; 8.7%)	4; 19.0%
	Ribociclib (n=5; 2.1%)	0; 0%
	Abemaciclib (n=4; 1.7%)	2; 50.0%
EGFR inhibitors (n=29; 12.0%)	Gefitinib (n=15; 6.2%)	5; 33.3%
	Afatinib (n=8; 3.3%)	6; 75.0%
	Erlotinib (n=4; 1.7%)	1; 25.0%
	Osimertinib (n=2; 0.8%)	0; 0%
mTOR inhibitors (n=41; 17.1%)	Everolimus (n=41; 17.1%)	6; 14.6%
iPARPs (n=10; 4.2%)	Niraparib (n=5; 2.1%)	0; 0%
	Olaparib (n=5; 2.1%)	1; 20%
VEGFR inhibitors (n=92; 38.3%)	Pazopanib (n=42; 17.5%)	20; 47.6%
	Sunitinib (n=14; 5.8%)	2; 14.3%
	Axitinib (n=8; 3.3%)	3; 37.5%
	Cabozantinib (n=8; 3.3%)	0; 0%
	Nintedanib (n=8; 3.3%)	5; 62.5%
	Regorafenib (n=5; 2.1%)	2; 40%
	Sorafenib (n=4; 1.7%)	4; 50%
	Tivozanib (n=2; 0.8%)	0; 0%
	Lenvatinib (n=1; 0.4%)	5; 33.3%
Other (n=13; 5.4%)	Dabrafenib (n=7; 2.9%)	1; 14.3%
	Lapatinib (n=3; 1.3%)	2; 66.7%
	Erdafitinib (n=1; 0.4%)	0; 0%
	Vemurafenib (n=1; 0.4%)	0; 0%
	Trametinib (n=1; 0.4%)	1; 100%

ALK anaplastic lymphoma kinase, *CDK* cyclin-dependent kinase, *EGFR* epidermal growth factor receptor, *iPARP* poly (ADP-ribose) polymerase inhibitors, *mTOR* mammalian target of rapamycin, *VEGFR* vascular endothelial growth factor receptor

first 2–3 weeks after initiation of treatment [3, 11, 16–18]. In studies where patients did not take antidiarrheal prophylaxis, diarrhea associated with afatinib affected 50–62% of patients within the first 7 days of starting therapy and 71% within the first 2 weeks [3]. Aw et al. observed that the median time to onset of diarrhea was 12 days for erlotinib and 3 days for afatinib [11].

The mean incidence of targeted OAA-induced diarrhea described in the SPC and in other studies, around 30–80% [2, 4, 6, 7, 16, 19, 20], is higher than we observed in our study. However, the method that we applied to collect the data is similar to that used in clinical trials. Therefore, regardless of the approach used, we think this difference in incidence could have two explanations. First, most studies do not include mTOR inhibitors or new families of TKIs, such as iPARPs, which have a lower incidence of diarrhea than other families, such as EGFR inhibitors or VEGFR inhibitors, i.e., the drugs included in most studies. We observed that 44.8% of patients treated with EGFR inhibitors had diarrhea. Pasaro et al. prospectively evaluated the incidence of diarrhea associated with EGFR inhibitors during the first 30 days of treatment using a methodology similar to ours. The authors used a questionnaire developed to enable patients to record data daily and observed an incidence of diarrhea of 57% (2% grades 3–4) for erlotinib, 12% (0% grades 3–4) for gefitinib, and 76% (12%) for afatinib [21]. Second, our knowledge and management of OAAs has improved over time compared with data from clinical trials. Early use of antidiarrheal drugs or, if necessary, reducing the dose of an OAA is essential for correct management of diarrhea. In our study, we observed that treatment with antidiarrheal drugs was started early, since 48.7% of loperamide was administered during the first 3 days after initiating the OAA.

Consistent with data reported elsewhere [21], we observed that only 3.3% of patients experienced severe diarrhea (grades 3–4). However, with some drugs, such as afatinib, this frequency reaches 10–15% for grade 3–4 diarrhea [4, 19]. Grade 3–4 diarrhea was ranked the second worst side effect

Table 2 Comparison of the main characteristics of patients according to the severity of diarrhea

		Grade 0—171 (71.2%)	Grades 1–2—61 (25.4%)	Grades 3–4—8 (3.3%)	Total—240 (100%)
Age, mean (SD), years		61.6 (13.1)	63.8 (13.0)	50.0 (11.6)*#	61.8 (13.2)
Sex, no. (%)	Male	53 (31.0%)	30 (49.2%)#	1 (12.5%)	84 (35.0%)
	Female	118 (69.0%)	31 (50.8%)	7 (87.5%)	156 (65.0%)
ECOG, no. (%)	0	116 (67.8%)	40 (65.6%)	6 (75.0%)	162 (67.5%)
	1	53 (31.0%)	20 (32.8%)	2 (25.0%)	75 (31.2%)
	2	2 (1.2%)	1 (1.6%)	0 (0.0%)	3 (1.3%)
Type of tumor, no. (%)	Breast cancer	55 (32.2%)	12 (19.7%)	1 (12.5%)	68 (28.3%)
	Renal carcinoma	40 (23.4%)	18 (29.5%)	0 (0.0%)	58 (24.2%)
	Non-small cell lung cancer	27 (15.8%)	13 (21.3%)	4 (50.0%)#	44 (18.3%)
	GIST	14 (8.2%)	7 (11.5%)	1 (12.5%)	22 (9.2%)
	Sarcoma	11 (6.4%)	5 (8.2%)	2 (25.0%)	18 (7.5%)
	Ovarian carcinoma	9 (5.3%)	1 (1.6%)	0 (0.0%)	10 (4.2%)
	Other	15 (8.8%)	5 (8.2%)	0 (0.0%)	20 (8.3%)
Abdominal and/or pelvic radiotherapy, no. (%)		6 (3.5%)	2 (3.3%)	0 (0.0%)	8 (3.3%)
Abdominal surgery, no. (%)		9 (5.3%)	3 (4.9%)	1 (12.5%)	13 (5.4%)
Celiac disease, no. (%)		3 (1.8%)	0 (0.0%)	0 (0.0%)	3 (1.3%)
Lactose intolerance, no. (%)		7 (4.1%)	1 (1.6%)	0 (0.0%)	8 (3.3%)
Type of OAA, no. (%)	VEGFR inhibitors	59 (34.5%)	30 (49.2%)	3 (37.5%)	92 (38.3%)
	mTOR inhibitors	35 (20.5%)	6 (9.8%)	0 (0.0%)	41 (17.1%)
	CDK inhibitors	25 (14.6%)	4 (6.6%)	1 (12.5%)	30 (12.5%)
	EGFR inhibitors	16 (9.4%)	10 (16.4%)	3 (37.5%)#	29 (12.1%)
	BCR-ALB inhibitors	10 (5.8%)	5 (8.2%)	0 (0.0%)	15 (6.3%)
	iPARP inhibitors	9 (5.3%)	1 (1.6%)	0 (0.0%)	10 (4.2%)
	ALK inhibitors	8 (4.7%)	1 (1.6%)	1 (12.5%)	10 (4.2%)
	Other	9 (5.3%)	4 (6.6%)	0 (0.0%)	
No. of concomitant medicines, mean (SD)		3.7 (3.0)	3.6 (3.0)	3.3 (3.7)	3.7 (3.0)
Full dose of OAA according to SPC, no. (%)		146 (85.4%)	55 (90.2%)	7 (87.5%)	208 (86.7%)
OAA taken with food, no. (%)		127 (74.3%)	34 (55.7%)#	2 (25.0%)#	163 (67.9%)

ALK anaplastic lymphoma kinase, *CDK* cyclin-dependent kinase, *ECOG* Eastern Cooperative Oncology Group, *EGFR* epidermal growth factor receptor, *GIST* gastrointestinal stromal tumor, *iPARP* poly (ADP-ribose) polymerase inhibitors, *mTOR* mammalian target of rapamycin, *OAA* oral antineoplastic agent, *SPC* summary of product characteristics, *VEGFR* vascular endothelial growth factor receptor

*Statistically significant differences with grades 1–2 ($P < 0.05$)

Statistically significant differences with grade 0 ($P < 0.05$)

after grade 3–4 nausea or vomiting related to anticancer drugs, having to consult a physician, or seeking treatment in an emergency room [7]. In serious cases, diarrhea can lead to dehydration, kidney failure, electrolyte imbalance, malnutrition, cardiovascular complications, sleep disturbance, and reduced quality of life. It may even be life-threatening [4]. For this reason, it is essential to identify and manage cases properly. It is more important in the case of OAAs, since these are long-term treatments that differ from classic chemotherapy, which is associated with adverse events that may continue to occur over time. Diarrhea should be specially monitored in older people; in addition to their greater vulnerability, we have observed a higher severity in diarrhea.

Our multivariate analysis revealed an association between a lower risk of diarrhea and taking the targeted OAA with food. Male sex and treatment with EGFR and VEGFR inhibitors were associated with a higher incidence of diarrhea, although the difference was not statistically significant. Published data on risk factors for diarrhea induced by anticancer drugs are inconsistent. Besides, most studies deal with classic chemotherapy and not with new targeted OAAs. Forde et al. found that the risk factors for diarrhea included frequency of dosing, concomitant abdominal and/or pelvic radiotherapy, concomitant use of more than one antineoplastic drug, older age, female gender, poorer performance status, bowel disease, and the presence of other comorbidities [8]. Ota et al. did not observe a correlation between the incidence of diarrhea and age and sex, although they did find that the severity of diarrhea in patients treated with fluoropyrimidines was significantly associated with the percentage of patients

Table 3 Correlation between the number of stools per day and some collected variables

Variables	*P*
Age	0.357
ECOG	0.394
Type of tumor	0.283
Abdominal surgery in the previous year	0.255
Abdominal and/or pelvic radiotherapy in the previous year	0.132
Celiac disease	0.575
Lactose intolerance	0.994
Number of concomitant medicines	0.343

with a small intestinal mucosal break [13]. However, in our study, we did not find any association between the incidence of diarrhea and the malabsorptive/intestinal inflammatory syndromes analyzed (celiac disease, lactose intolerance, or previous surgery or radiotherapy). Another study found that patient age, presence of skin metastases at baseline, initiation of treatment in spring, earlier cycles, and grade 1 diarrhea in the previous cycle were significant predictors for ≥ grade 2 diarrhea [22]. Aw et al. observed that low body weight (< 50 kg), female gender, and baseline renal impairment (creatinine clearance ≤ 80 mL/min) were associated with a higher incidence of diarrhea [11].

With OAAs, patients are ultimately responsible for taking the medication. Some patients, in the hope of increasing treatment effectiveness, will continue to take their tablets despite the onset of severe diarrhea. It is crucial that healthcare professionals inform patients appropriately about the risks involved and about importance of self-management of diarrhea as they commence a new course of targeted OAAs. Of particular interest are situations associated with higher incidence, such as taking the OAA on an empty stomach or treatment with EGFR or VEGFR inhibitors. All patients should be given a regimen-based information sheet outlining potential side effects written in simple language [6]. Adequate management of diarrhea minimizes its impact and reduces differences in incidence between targeted OAAs [21].

Our study is limited by the fact that we did not assess the impact of diarrhea on patients' quality of life. The patient's perception of the burden of their toxicity might differ from the classic medical description of its severity [23, 24]. We think future studies should also collect this kind of adverse events through patient-reported outcomes measures, such as PRO-CTCAE questionnaire [24], because there is often no correlation between the toxicity reported by patients and that assessed by health professionals [25]. Selection bias could be another limitation, since 21.1% of patients were lost to follow-up, thus highlighting the difficulty of conducting studies with large amounts of data collected prospectively from patients. Thus, our results reflect standard clinical practice. We used a 30-day follow-up to facilitate data collection, since diarrhea appears frequently within the first 2–3 weeks after initiation of treatment [3, 11, 16–18].

In conclusion, more than a third of patients in treatment with OAAs presented diarrhea (any grade), and 22.1% of stools were semi-liquid/liquid. A higher incidence of diarrhea was recorded in patients treated with EGFR and VEGFR inhibitors. Remarkably, taking the OAA on an empty stomach was statistically significantly associated with an increased risk of developing diarrhea in a multivariate analysis. Education on proper identification and management of diarrhea should be provided to patients at initiation of OAA.

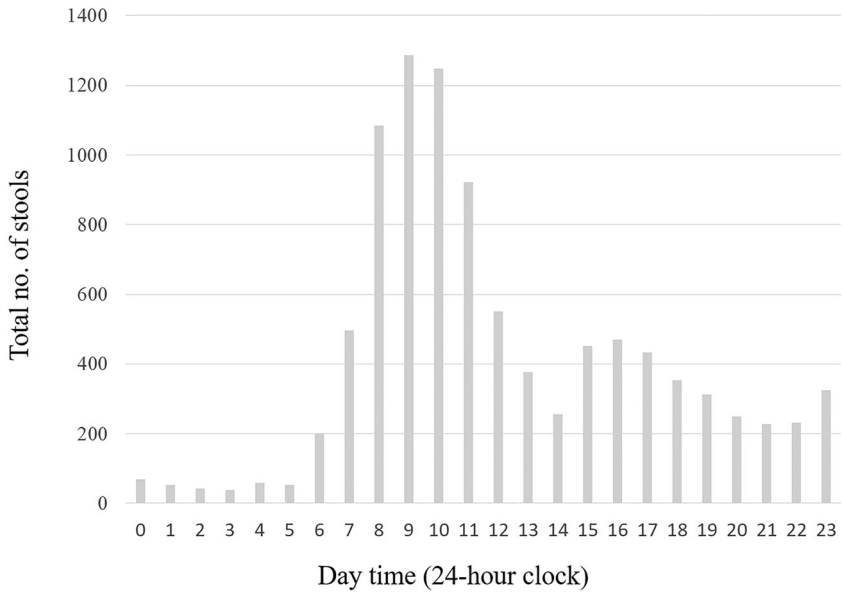

Fig. 2 The total number of stools (all patients) at different times of the day during the follow-up period

Table 4 Multivariate analysis of factors associated with the occurrence of diarrhea

Variable		OR	CI (95%)	*P* value
Age		0.99	0.97–1.03	0.939
Sex	Female	0.87	0.42–1.79	0.701
ECOG*	1	0.93	0.44–1.94	0.844
	2	3.33	0.24–45.45	0.368
Type of tumor**	Breast cancer	2.84	0.28–29.10	0.380
	Non-small cell lung cancer	2.59	0.31–21.40	0.378
	GIST	2.91	0.57–14.73	0.197
	Sarcoma	0.61	0.40–5.18	0.429
	Ovarian carcinoma	0.00	0.00–NA	0.999
	Other	2.08	0.35–12.27	0.420
Type of OAA***	mTOR inhibitors	0.13	0.01–1.22	0.074
	CDK inhibitors	0.15	0.01–1.74	0.131
	EGFR inhibitors	1.40	0.58–3.39	0.453
	BCR-ALB inhibitors	0.57	0.10–3.27	0.527
	iPARP	0.00	0.00–NA	0.999
	ALK inhibitors	0.28	0.02–3.64	0.329
	Other	0.24	0.03–2.10	0.199
OAA taken with food		0.41	0.21–0.96	0.038

ALK anaplastic lymphoma kinase, *CDK* cyclin-dependent kinase, *ECOG* Eastern Cooperative Oncology Group, *EGFR* epidermal growth factor receptor, *GIST* gastrointestinal stromal tumor, *iPARP* poly (ADP-ribose) polymerase inhibitors, *OAA* oral antineoplastic agent, *VEGFR* vascular endothelial growth factor receptor

*ECOG (0 *ref*)

**Type of tumor (renal carcinoma *ref*)

***Type of OAA (VEGFR inhibitors *ref*)

Authors' contribution Dr. Martín and Dr. Escudero-Vilaplana conceived the idea. Dr. Escuero-Vilaplana, Dr. Collado-Borrell, Dr. del Monte-Millán, Dr. Gómez, Dr. Revuelta-Herrero, Dr. Hoyo-Muñoz, Dr. Marzal-Alfaro, Dr. Gonzalez-Haba, Dr. Lopez-Tarruella, and Dra. Jerez performed the measurements and collected the data. Dr. Herranz, Dr. Sanjurjo, and Dr. Martín were involved in planning and supervised the work. Dr. Escudero-Vilaplana, Dr. Collado-Borrell, and Dr. del Monte-Millán processed the experimental data, performed the analysis, drafted the manuscript, and designed the figures. Dr. Martín, Dr. Herranz, and Dr. Sanjurjo aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

Data availability N/A

Declarations

Ethics approval and consent to participate The study was approved by the local ethics committee (study code MMJ-ITK-2013-01) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Patients signed an informed consent before entering the study and for publication.

Consent for publication Patients signed an informed consent before entering the study and for publication.

Conflict of interest Dr. Escudero-Vilaplana received support to continuing education/advisory fees from Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Ipsen Pharma, Janssen and Merck Sharp & Dohme, Novartis, and Pfizer, outside the submitted work.

Dr. Collado-Borrell received support to continuing education/advisory fees from Boehringer ingelheim, Hoffmann-La Roche, Bristol-Myers Squibb, Janssen Cilag, and Pfizer, outside the submitted work.

Dr. Marzal-Alfaro received support to continuing education/advisory fees from Roche, Abbvie, Pfizer, and Bayer Hispania, outside the submitted work.

Dr. Gonzalez-Haba received support to advisory fees from Bayer, Bristol-Myers Squibb, and Novartis, outside the submitted work.

Dr. Lopez-Tarruella Cobo has received consulting/advisory fees from Celgene, Novartis, Pierre Fabre, Pfizer, Roche, Astra-Zeneca, Eisai, Daiichi-Sankyo, and Lilly and speakers' honoraria from Lilly, Novartis, and Pfizer, outside the submitted work.

Dr. Jerez Gilarranz has a consultant or advisory role at Novartis, Pfizer, Roche, and AstraZeneca and has received speaker honoraria from Roche, Novartis, and AstraZeneca and travel grants from Roche, Novartis, Pfizer, and Teva.

Dr. Herranz reported honorary/advisory fees from Astellas, Janssen, Kern, and Novartis, outside the submitted work.

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Code availability N/A

References

1. IMS Institute for Healthcare Informatics (2016) Global oncology trend report. A review of 2015 and outlook to 2020
2. Escudero-Vilaplana V, Revuelta-Herrero JL, Collado-Borrell R, Marzal-Alfaro B, Gimenez-Manzorro A, Herranz-Alonso A, Sanjurjo-Saez M (2019) Oral antineoplastic agents: assessment of safety and dose adjustments in clinical practice. Expert Opin Drug Saf 18(9):861–868
3. Ota K, Takeuchi T, Kojima Y, Harada S, Ozaki H, Sugawara N, Hirata Y, Yamaguchi T, Terazawa T, Kakimoto K, Kii T, Goto M, Higuchi K (2019) Fluorepyrimmide-induced intestinal mucosal injury is associated with the severity of chemotherapy-related diarrhea. Scand J Gastroenterol 54(2):227–232
4. Pessi MA, Zilembo N, Haspinger ER, Molino L, di Cosimo S, Garassino M, Ripamonti CI (2014) Targeted therapy-induced diarrhea: a review of the literature. Crit Rev Oncol Hematol 90(2):165–179
5. Rugo HS, Di Palma JA, Tripathy D et al (2019) The characterization, management and future considerations of ErbB-family TKI-associated diarrhea. Breast Cancer Res Treat 175(1):5–15
6. Andreyev J, Ross P, Donnellan C et al (2014) Guidance on the management of diarrhea during cancer chemotherapy. Lancet Oncol 15(10):e477–e460
7. Tarricone R, Abu Koush D, Nyanzi-Wakholi B, Medina-Lara A (2016) A systematic literature review of the economic implications of chemotherapy-induced diarrhea and its impact on quality of life. Crit Rev Oncol Hematol 99:37–48
8. Forde C (2017) Systemic anti-cancer therapy-induced diarrhea. Br J Hosp Med (Lond) 78(9):C135–C139
9. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. Bethesda, Md. U.S. Department of Health and Human Services, National Institutes of Health, 2017. National Cancer Institute
10. Richardson G, Dobish R (2007) Chemotherapy induced diarrhea. J Oncol Pharm Pract 13(4):181–189
11. Aw DC, Tan EH, Chin TM et al (2018) Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. Asia Pac J Clin Oncol 14(1):23–31
12. Davila M, Bresalier RS (2008) Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastroenterol Hepatol 5(12): 682–696
13. Iacovelli R, Pietrantonio F, Palazzo A, Maggi C, Ricchini F, de Braud F, di Bartolomeo M (2014) Incidence and relative risk of grade 3 and 4 diarrhoea in patients treated with capecitabine or 5-fluorouracil: a meta-analysis of published trials. Br J Clin Pharmacol 78(6):1228–1237
14. Barcenas CH, Hurvitz SA, Palma JAD et al (2020) Improved tolerability of neratinib in patients with HER2-positive early-stage breast cancer: the CONTROL trial. Ann Oncol 31(9):1223–1230
15. Xu C, Ravva P, Dang JS, Laurent J, Adessi C, McIntyre C, Meneses-Lorente G, Mercier F (2018) A continuous-time multistate Markov model to describe the occurrence and severity of diarrhea events in metastatic breast cancer patients treated with lumretuzumab in combination with pertuzumab and paclitaxel. Cancer Chemother Pharmacol 82(3):395–406
16. Cheema PK, Thawer A, Leake J, Cheng SY, Khanna S, Charles Victor J (2019) Multi-disciplinary proactive follow-up algorithm for patients with advanced NSCLC receiving afatinib. Support Care Cancer 27(3):1029–1039
17. Chan A, Delaloge S, Holmes FA, ExteNET Study Group et al (2016) Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 17(3):367–377
18. Johnston SRD, Harbeck N, Hegg R et al (2020) Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2-, node-positive, high-risk, early breast cancer (monarchE). J Clin Oncol 20:JCO2002514
19. Leboulleux S, Bastholt L, Krause T et al (2012) Vandetanib in locally advanced or metastatic differenciated thyroid cancer: a randomized, double-blind, phase 2 trial. Lancet Oncol 123(9):897–905
20. European Public Assessment Reports. Amsterdam: European Medicines Agency. Available at: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_medicine [Accessed in July 2020]
21. Passaro A, Di Maio M, Del Signore E et al (2014) Management of nonhematologic toxicities associated with different EGFR-TKIs in advanced NSCLC: a comparison analysis. Clin Lung Cancer 15(4): 307–312
22. Dranitsaris G, Lacouture ME (2014) Development of precition tools for diarrhea and rash in breast cancer patients receiving lapatinib in combination with capcitabine. Breast Cancer Res Treat 147(3):631–638
23. Carlotto A, Hogsett VL, Maiorini EM, Razulis JG, Sonis ST (2013) The economic burden of toxicities associated with cancer treatment: review of the literature and analysis of nausea, vomiting, diarrhoea, oral mucositis andfatigue. Pharmacoeconomics 31:753–766
24. Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), Version 1.0. Bethesda, Md. U.S. Department of Health and Human Services, National Institutes of Health, 2017. National Cancer Institute
25. Di Maio M, Gallo C, Leighl NB et al (2015) Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 33(8):910–915