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Effectiveness of a standardized patient education program on therapy-related side effects and unplanned therapy interruptions in oral cancer therapy: a cluster-randomized controlled trial

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Abstract
Purpose Oral agents for cancer treatment are increasingly prescribed due to their benefits. However, oral cancer medications are difficult to handle and have a considerable potential for side effects. This type of therapy requires a high level of self-management competence by the patient. A standardized patient education program provided by physicians and oncology nurses may positively influence the handling of oral agents. The aim of the study was to evaluate the impact of a standardized patient education program provided by specially trained oncology nurses on therapy management regarding side effects and unplanned therapy interruptions.
Methods One hundred sixty-five patients from 28 office-based oncology practices from all over Germany participated in this cluster-randomized controlled study. Patients of both intervention (n = 111) and standard care groups (n = 54) received the usual oncologist counseling; in addition, the patients from the intervention group (k = 17 practices) received an education from specially trained oncology nurses. The time of observation was 3 months per patient.
Results The patients of the intervention group reported fewer side effects (skin rash, pain, fatigue, nausea, vomiting). Patients in the standard care group interrupted the therapy more frequently without informing their oncologist, compared to the intervention group.
Conclusions Patients benefit from a standardized patient education program provided by specially trained oncology nurses. They tend to handle side effects and critical situations better.

Keywords Oral cancer therapy • Patient education • Oncology nurses • Therapy-related side effects • Unplanned therapy interruption

Introduction

Outpatient oncology care is undergoing a profound change. New oral cancer drugs are continuously approved and complement or replace intravenous chemotherapy. From 2011 to 2014, 25 new oral agents were approved by the US Food and Drug Administration (FDA) [1]. About 25% of all hematology-oncology drugs in development are designed for oral administration [1–3]. Based on estimations by the Scientific Institute of Office-Based Hematologists and Oncologists (WINHO), more than 40% of the patients undergoing cancer therapy in ambulant care in Germany receive oral agents [4]. These drugs revealed a great potential in cancer care. For example, the approval of imatinib (Glivec®) in 2001 for the therapy of chronic myeloid leukemia induced a 30% decrease in mortality [5]. On the one hand, this advancement of therapy is an important step in cancer treatment. On

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the other hand, it poses a challenge for oncology care [6]. In the case of intravenous chemotherapy, the drug is administered under the supervision of the oncology team. When it comes to oral agents, however, the place of treatment is the patient's home. In this treatment setting, correct treatment management cannot be guaranteed without first identifying the patients' needs in order for the patients to be empowered and become an expert in their own treatment because cancer therapies are commonly difficult to handle and the medication often shows a high risk of side effects and interactions with other drugs [3, 7, 8]. Care providers are challenged by the question of how patients, who are mostly elderly and multimorbid, and their supporting relatives can be equipped with essential competencies to manage their treatment independently. Before patients start their cancer therapy, they are usually provided with information about the treatment by their physician [9]. However, patients often feel overwhelmed by all the details in this stressful situation and tend to have a reduced capacity to assimilate complex information [10]. Education and additional support at the beginning and in the course of the treatment can be a useful approach for patients to better handle this situation [1, 10–14].

Recent studies showed the positive impact supportive care programs provided by nurses can have on patients [3, 11, 15–17]. Patient-focused motivation techniques and education performed by nurses are suitable to strengthen the patients' understanding of risks and benefits of the anti-cancer treatment and oral agents [3]. These care programs can prevent an incorrect medication intake due to misunderstandings [18], lead to a decrease in treatment-related symptoms like pain and fatigue, and reduce critical events [3, 11]. In addition, patient education can facilitate supportive care through a better communication between patient and healthcare provider, and it may advance the early detection of adverse toxicity events and foster rapid symptom management [15].

Goal

The aim of our study was to evaluate the effectiveness of a standardized patient education program provided by specially trained oncology nurses on therapy management regarding side effects and unplanned therapy interruptions in outpatient oncology care.

Patients and methods

A prospective cluster-randomized trial was conducted. The study was approved by the ethics committee of the Bavarian medical chamber. The study was the main part of the project *Patients' Competence in Oral Cancer Therapy (PACOCT)*, which was funded by the German Federal Ministry of Health within the National Cancer Plan. Beside the intervention study, a patient education program provided by oncology nurses, we surveyed the current situation of patients undergoing oral anti-cancer therapy and the current situation of patient education and cancer therapy with oral agents in outpatient oncology practices. Furthermore, we aimed to identify structural and organizational needs for a standardized patient education program.

Setting and sample

All oncology practices from the WINHO network (k = 196 practices) were invited to participate in the study. The WINHO Network is a unique union of outpatient oncology practices from all over Germany for scientific collaboration. The practices which agreed to participate in the study (k = 28) were randomized on practice level (2:1) into an intervention and a standard care group. Accordingly, cluster-wise randomized patients were assigned to the groups depending on the practice's assignment. Patients were recruited during an 8-month period, from March until October 2014, and gave their informed consent prior to study participation. Patients were observed at baseline (T0) and through four follow-up periods (T1–T4) over a span of 3 months between March and December 2014. The recruitment flow is shown in Fig. 1.

Patients were included if they were aged 18 years or older, newly adjusted on an oral anti-cancer therapy (i.e., no prior oral anti-cancer therapy; prior intravenous cancer therapies were permitted), not receiving concurrent intravenous anti-cancer therapy, and receiving oral agents which were approved by the German or the European drug authorities (BfArM/EMA). Patients with an anti-hormone therapy were only included if they had metastatic breast cancer or metastatic prostate cancer. Patients with a long-term solely adjuvant anti-hormone therapy were excluded. Patients who fit the criteria were approached and informed about the subject of the study by their physicians before the start of therapy.

Sample size

A sample size calculation was done which assumed that for a two-tailed group comparison at the $p < 0.05$ significance level and a minimum effect size of 0.3, 176 patients per group would be necessary to achieve a power of 80%. In virtue of the intracluster design, we also calculated the design effect using 0.01 as an estimate of intracluster correlation. This value was used as median in an analysis of 31 cluster-based studies in primary care [19] and seems suitable as an approximation for oncology practices. The design effect was calculated with 1.19, which means that a

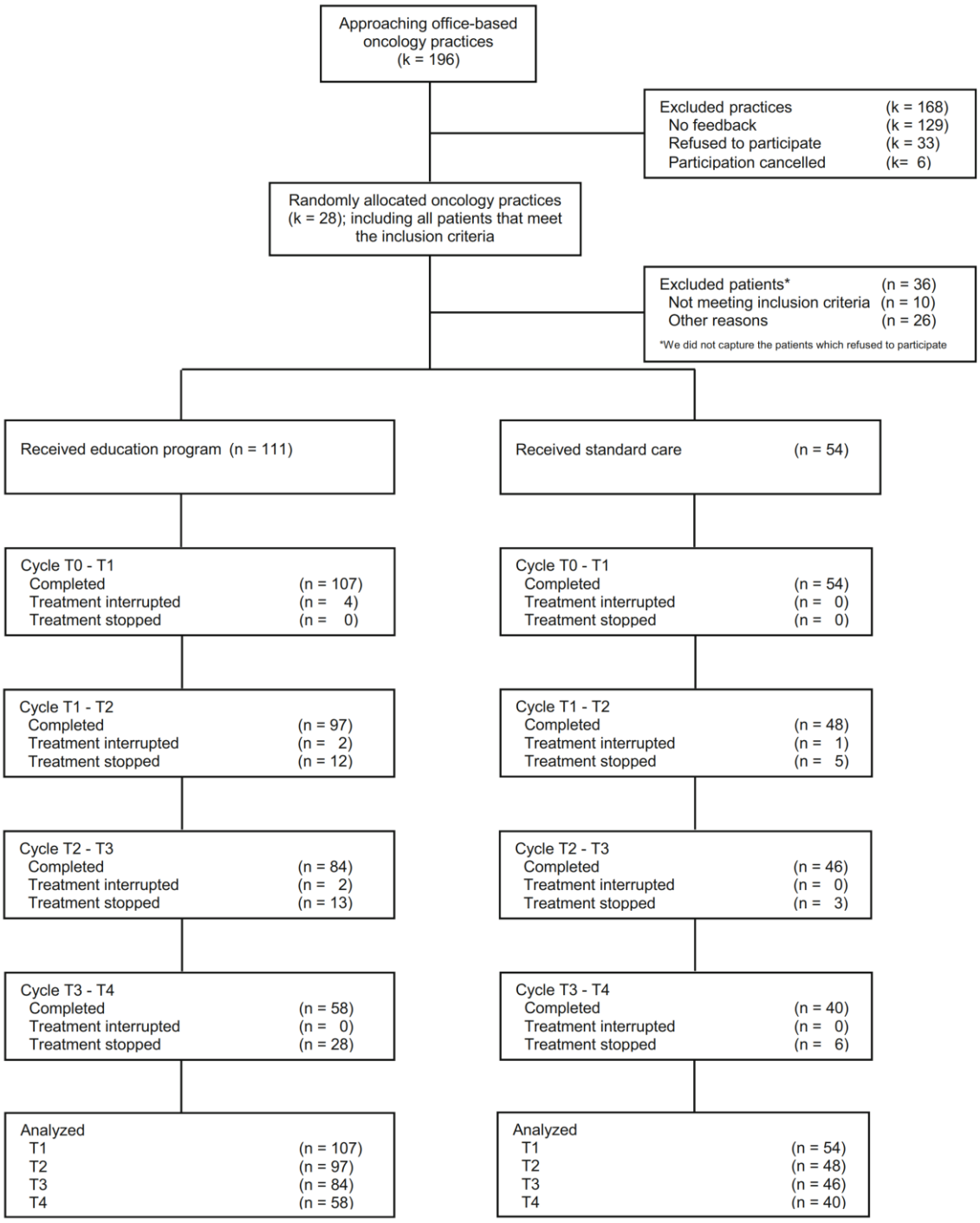

Fig. 1 Study recruitment flow

minimum of 210 patients were required. Therefore, each practice was asked to recruit 20 patients.

Standard care

In the standard care group, patients were routinely informed about the treatment, the drug, and the adverse effects by the physician. For the duration of the study, patients scheduled regular treatment appointments as they would have outside a study. Study nurses in the standard care group received an online briefing about the use of the measuring instruments. For side effect documentation, a self-developed diary was used. The sociodemographic and clinical characteristics of the sample were documented by the nurses.

Intervention

The patients in the intervention group took part in a patient education program provided by oncology nurses. This program was developed on the basis of the MOATT—the Oral Agent Teaching Tool from the Multinational Association of Supportive Care in Cancer (MASCC). This care program conversation guide addresses medication-specific topics like the shape and look of the pills, intake routine, storage, drug interactions, side effect prevention, and other daily clues for the patient [20]. Furthermore, a standardized form covering these topics was to be filled out jointly by patients and nurses. Prior to the study, oncology nurses of the intervention group were trained in relevant subjects like motivational conversation techniques, action mechanisms of the drugs, research strategies, and usage of the study instruments. The patient- and medication-specific guidance provided by the nurses was to address the patients' needs and social resources and go beyond standard patient information. After the patient received general information and training from the physician with regards to treatment when starting therapy, patient and nurse arranged an appointment for the first education session within 1 week. In preparation for the first session, the patient was asked to fill out a self-assessment sheet concerning health literacy, expected adherence, social background, care dependency, depression, and geriatric situation. Based on all available information including the patient's chart and the medication plan, the nurses structured the first patient- and medication-specific education session. The first patient education session (T0) was not to take more than 45 min. At first, the patient information previously provided by the physician was repeated. On this basis, nurses had to conduct the education session and communicate the medication-specific contents for each patient. This patient education was repeated during all follow-up appointments. The first two appointments (T1 and T2) were scheduled at an interval of 2 weeks, the further appointments (T3, T4) with a gap of 4 weeks. The duration of these follow-up appointments was not to exceed 30 min. The measurement instruments were the same for the intervention group as for the standard care group.

Outcome measures

As outcomes, frequencies of therapy-related side effects (i.e., skin rash, pain, nausea, vomiting, fatigue, and diarrhea) were surveyed on a daily basis during the intervention cycle through a diary. Furthermore, we surveyed the frequency of unplanned therapy interruptions (UTI). In order to obtain more details about UTI, we asked whether they were initiated by the physician or by the patient. Therapy interruptions were monitored at each time of measurement during the intervention. To collect these data, the study nurses had to keep all outcomes on record. On the patient side, we used a diary for side effects.

Data analysis

The analysis of side effects is based on the diaries that were kept by the patients from both groups. For each time of measurement, we counted the number of reported side effects in the preceding period. The number of side effects at T1 reflects the frequency of side effects between T0 and T1. Consequently, the number of side effects is a count variable, which can be analyzed using a Poisson regression. However, one assumption of this model is that the mean of the outcome variable equals the variance [21]. Here, for all side effects, the variance of the respective count variable is much larger than the mean, which is known as overdispersion. To overcome this issue, we used the more appropriate negative binomial regression model [21]. Another issue concerns the repeated measurements (T1–T4), which violate the independence assumption that most statistical models rely on and usually result in standard errors that are too small. We estimated clustered standard errors to correct for this issue. The statistical analyses were performed using R 3.3.1 [22] and Stata 14.1.

To test for differences in side effects between the control and the intervention group, negative binomial regression models were estimated. Based on these estimations, the predicted counts for each group as well as the predicted differences between the groups' counts for each of the four times of measurement (T1–T4) were computed. The results are shown in Fig. 2. Additional models were estimated that include time, i.e., the time of measurement, as a linear and a squared term to test for nonlinear effects (u-shaped or inverted u-shaped effects). In these polynomial regressions, the grouping (control vs. intervention) variable was included as an interaction term to test for differences in the progression of the side effects.

In terms of UTI, three possible outcomes can be distinguished. First, no UTI occurred. Second, the oncologist advised the patient to interrupt the therapy. Third, the patient decided to interrupt the therapy by him-/herself. To estimate the chances for the three outcomes for each time of measurement, we calculated odds ratios for the intervention and for the standard care group.

Results

In total, we recruited 165 patients from 28 oncology practices from all over Germany. For the intervention group, 111 patients were recruited and 54 patients for the standard care group (Fig. 1). The mean age in the intervention group was 69.32 years (SD = 12.31) and 71.35 years in the standard care group (SD = 10.9). While gender was equally distributed in

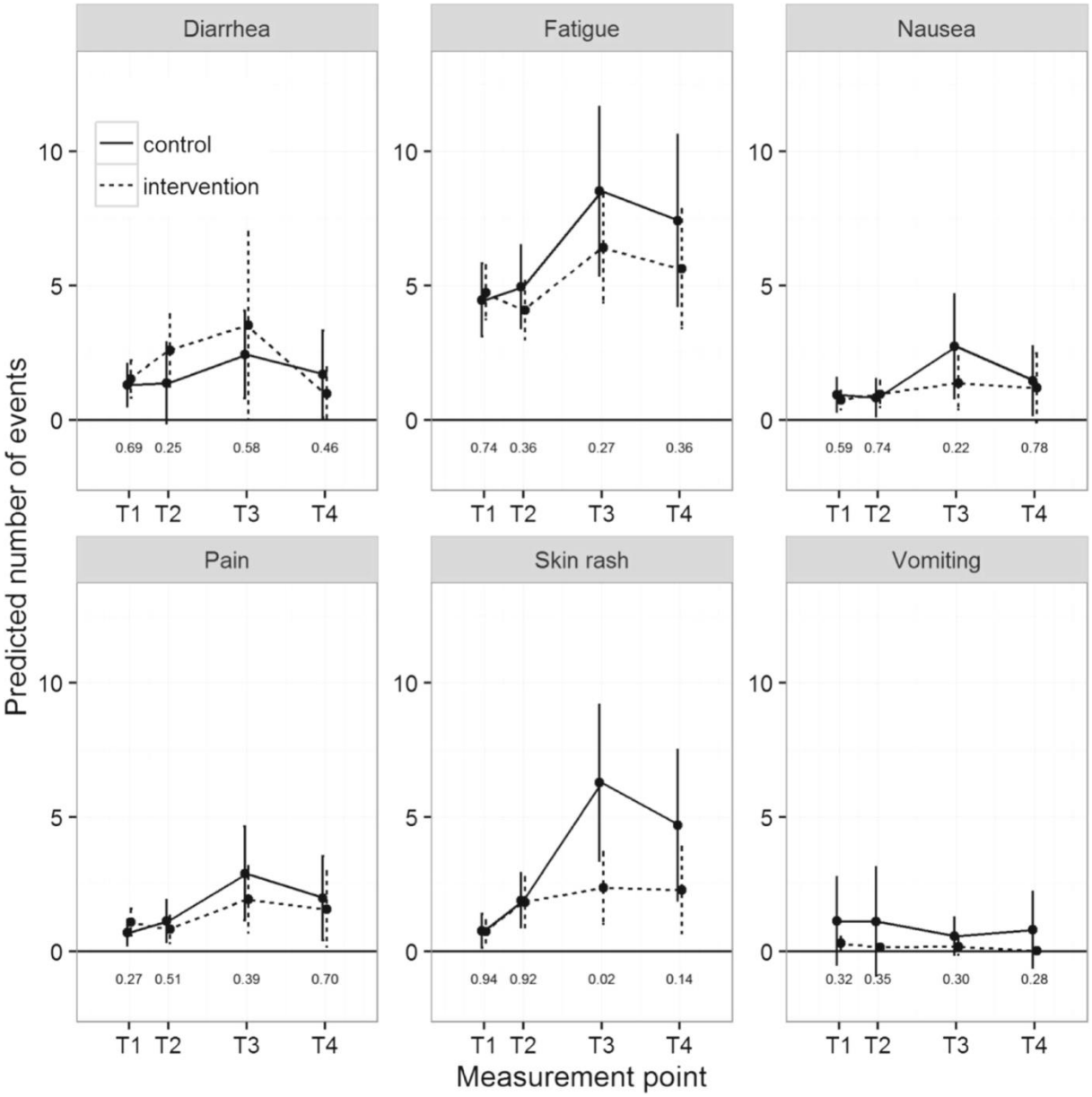

Fig. 2 Predicted number of events. Note: values at the bottom of the plots denote *p* values for group differences between standard care and intervention group

the standard care group (50.0% *n* = 27, 50.0% *n* = 27), women (55.9%, *n* = 62) were overrepresented in the intervention group (men 44.1%, *n* = 49). In both groups, most of the patients lived in a relationship (intervention 70.1%, standard care 77.4%). The most frequent diagnoses were colon cancer (intervention 12.9%, standard care 20.8%), myeloproliferative neoplasms (intervention 14.9%, standard care 8.3%), breast cancer (intervention 11.9%, standard care 6.2%), and lung cancer (intervention 6.9%, standard care 10.4%). The most frequently prescribed agents were capecitabine (intervention 25.2%, standard care 30.2%), hydroxyurea (intervention 20.7%, standard care 7.5%), temozolomide (intervention 9.9%, standard care 3.8%), lenalidomide (intervention 4.5%, standard care 9.4%), and erlotinib (intervention 4.5%, standard care 9.4%) (Table 1).

Side effects

Figure 2 illustrates the predicted numbers of each side effect. The *y*-axis shows the predicted number of side effects for standard care and the intervention group across the four follow-up points. In almost all instances, the intervention group tended to experience fewer side effects for fatigue, nausea, pain, skin rash, and vomiting (exception: diarrhea) than the standard care group. Especially the curves for fatigue and skin rash underline these findings. However, despite the observable trend to fewer side effects, there was only one statistically significant difference between the groups. The intervention group reported at T3 (8 weeks after treatment start) significantly fewer skin rash ($p = 0.02$) than the standard care group. In reference to the trends toward fewer side effects, almost all plots of the

Table 1 Sociodemographic and clinical characteristics of the sample

	Standard care		Intervention	
	%	*n*	*%*	*n*
Women	50.0	27	55.9	62
Men	50.0	27	44.1	49
Age (mean)	71.35 (SD = 10.9)		69.32 (SD = 12.31)	
Single	20.8	11	28.3	30
In a relationship	77.3	41	70.7	75
Care home	1.9	1	1.0	1
Entity (ICD10)				
C16—Malignant neoplasm of stomach	0.0	0	2.0	2
C17—Malignant neoplasm of small intestine	0.0	0	1.0	1
C18—Malignant neoplasm of colon	20.8	10	12.9	13
C20—Malignant neoplasm of rectum	2.1	1	8.9	9
C22—Malignant neoplasm of liver and intrahepatic bile ducts	4.2	2	3.0	3
C25—Malignant neoplasm of pancreas	2.1	1	0.0	0
C34—Malignant neoplasm of bronchus and lung	10.4	5	6.9	7
C41—Malignant neoplasm of bone and articular cartilage of other and unspecified sites	0.0	0	1.0	1
C43—Malignant melanoma of skin	4.2	2	0.0	0
C50—Malignant neoplasm of breast	6.2	3	11.9	12
C56—Malignant neoplasm of ovary	2.1	1	1.0	1
C61—Malignant neoplasm of prostate	8.3	4	2.0	2
C64—Malignant neoplasm of kidney, except renal pelvis	4.2	2	4.0	4
C71—Malignant neoplasm of brain	4.2	2	9.9	10
C76—Malignant neoplasm of other and ill-defined sites	0.0	0	1.0	1
C90—Multiple myeloma and malignant plasma cell neoplasms	8.3	4	5.9	6
C91—Lymphoid leukemia	4.2	2	0.0	0
C92—Myeloid leukemia	6.2	3	6.9	7
C93—Monocytic leukemia	0.0	0	1.0	1
C94—Other leukemias of specified cell type	0.0	0	1.0	1
D45—Polycythaemia vera	0.0	0	4.0	4
D46—Myelodysplastic syndromes	2.1	1	0.0	0
D47—Other neoplasms of uncertain or unknown behavior of lymphoid, hematopoietic, and related tissue—myeloproliferative neoplasms	8.3	4	14.9	15
D75—Other diseases of blood and blood-forming organs	0.0	0	1.0	1
K63—Other diseases of intestine	2.1	1	0.0	0
Agent				
Capecitabine	30.2	16	25.2	28
Hydroxyurea	7.5	4	20.7	23
Temozolomide	3.8	2	9.9	11
Lenalidomide	9.4	5	4.5	5
Erlotinib	9.4	5	4.5	5
Imatinib	3.8	2	3.6	4
Pazopanib	5.7	3	1.8	2
Everolimus	0.0	0	4.5	5
Sorafenib	3.8	2	2.7	3
Abiraterone	7.5	4	0.9	1
Regorafenib	1.9	1	2.7	3

Table 1 (continued)

	Standard care		Intervention	
	%	*n*	*%*	*n*
Sunitinib	1.9	1	2.7	3
Vemurafenib	5.7	3	0.0	0
Treosulfan	1.9	1	0.9	1
Exemestane	1.9	1	0.9	1
Nilotinib	0.0	0	1.8	2
Afatinib	0.0	0	1.8	2
Dasatinib	0.0	0	1.8	2
Chlorambucil	3.8	2	0.0	0
Pomalidomide	0.0	0	1.8	2
Gefitinib	0.0	0	0.9	1
Lapatinib	0.0	0	0.9	1
Enzalutamide	0.0	0	0.9	1
Etoposide	0.0	0	0.9	1

Note: For these analyses, the statement “no response” was not considered

intervention group follow an inverted u-shaped curve over time. For fatigue and pain, we found trends for slower increase in side effects over time, i.e., the interaction between the linear time variable and the groups.

Therapy interruption

To estimate the chances for the three outcomes regarding therapy interruption at each time of measurement, we calculated odds ratios for the intervention and the control group. Since almost none of the odds ratios are statistically different from 1, we describe mere trends. The first outcome “No UTI” is the reference category. For T1 and with respect to the first outcome No UTI, the intervention group has a 1.93 times higher chance to experience an oncologist’s advised UTI than the control group; at T2 even a 2.36 higher chance, before the trend decreases (T3 1.66, T4 1.53). By contrast, the chance to experience a patient-initiated UTI is lower for the intervention group. Across the four times of measurement, a clear trend can be noticed. The intervention group always has higher chances to not experience a patient-initiated UTI, especially at T1 0.14 (p = 0.01) (T2 0.71, T3 0.33, T4 0.45) (Table 2).

Discussion

This cluster-randomized trial aimed to investigate the effectiveness of a standardized patient education program in oral cancer care provided by oncology nurses in the outpatient setting. The results elucidate that a patient education program can help to reduce therapy-related side effects of fatigue, nausea, pain, skin rash, and vomiting, and to reduce unplanned therapy interruptions without the physicians’ involvement. These effects can be achieved with the aid of minimal additional resources of time from the physician. These trends correspond to findings from other trials which integrate a patient education program provided by nurses in oncology care and also reported better symptom management and fewer critical events [11, 15, 23]. In contrast to most of these studies, we focused on the critical event “unplanned therapy interruption” instead of, e.g., hospitalization rate.

The therapy-related side effects mainly occurred between the start of therapy and T3 (8 weeks). While the side effects in the intervention group remained stable during T1 and T2, the side effects in the control group increased until T3 (Fig. 2). Hence, the most crucial time for a supportive care intervention in oral cancer therapy seems to be in the first 2 months after the treatment has started, which is supported by a previous study from Molassiotes et al. [11]. When starting therapy, patients receive plenty of information about their treatment by their physician and others. Patients often cannot digest and assimilate all the information in a short time [10, 24]. An education program and additional support from nurses seem to be useful in oncology care for framing this situation, to meet patients’ needs appropriately and overcome communication limits of the patient [1, 10–14]. Through the education program, the patient is continuously monitored by the oncology nurse. This frequent contact with the patients enables oncology nurses and physicians to provide early detection and intervention concerning adverse events, especially in the case of new drugs with a broad spectrum of less well-known effects [3, 15, 25]. A continuous monitoring can protect oncology patients from therapy-related side effects, e.g., skin rash, hand-foot syndrome, nausea, and vomiting [26–28].

Table 2 Therapy interruptions

	T1	T2	T3	T4
No unplanned therapy interruptions	1	1	1	1
Unplanned therapy interruptions: oncologist	1.93 (0.52, 7.21) $p = 0.34$	2.36 (0.49, 11.41) $p = 0.30$	1.66 (0.50, 5.50) $p = 0.43$	1.53 (0.43, 5.44) $p = 0.53$
Unplanned therapy interruptions: patient	0.14 (0.03, 0.69) $p = 0.01$	0.71 (0.15, 3.27) $p = 0.66$	0.33 (0.07, 1.47) $p = 0.16$	0.45 (0.12, 1.75) $p = 0.27$
N	159	143	128	97

Note: intervention vs. standard care group (odds ratios, 95% CI; "No unplanned therapy interruptions" = reference category)

The close contact with the oncology nurse and the physician may have an additional benefit for the patient, because it has the potential to improve the patient-physician collaboration [29]. The study showed that unplanned therapy interruptions by recommendation of the physician occurred more often in the intervention group. Through continuous monitoring, the physician has the ability to adjust or interrupt the therapy if necessary and prevent further side effects [16, 30]. In the control group, patients decided more often to interrupt the therapy without informing the physician. This may indicate that the patients in the intervention group were better able to react adequately at times of critical events.

Our study is limited in that it can only reveal trends. Measurable effects are small, and since we did not achieve the expected number of patients in both groups, namely, at least 20 patients in every attending practice and altogether 560 patients, the resulting evidence is restricted. There are few significant differences between the groups. Future studies should repeat the trial with a larger sample. Due to the fact that our trial included a large number of oral agents and types of cancer, the subgroups of patients were often too small to get reliable data on specific oral agents and cancer types. The analysis regarding side effects and unplanned therapy interruptions was only conducted for the two study groups and not on single oral agents or types of cancer. Therefore, we are only able to give a general statement on the effectiveness of a standardized patient education program.

The findings of our trial show the great potential of a nurse-performed standardized patient education program in oral cancer therapy. Further studies should address the specific needs of different patient groups to improve proactive therapy management. This could for example be achieved by handing out a questionnaire to the patients which asks for important aspects from their point of view. Additionally, research should focus on more specifically defined disease situations (i.e., solid tumors, leukemias, etc.) and probably age subgroups. Furthermore, in order to make patient education programs in oncology more popular and sophisticated, their impact on hard clinical end points (e.g., progression-free survival and overall survival) and cost-effectiveness have to be evaluated.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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