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Adherence and patients' experiences with the use of oral anticancer agents

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Abstract

A rapidly growing number of oral anticancer agents has become available in oncology and hematology. Though these introductions have several benefits, medication adherence is an issue of concern. Little is known about the factors influencing adherence to treatment with oral anticancer agents in daily practice. *Material and methods.* In this observational, multicenter study including 216 patients, carried out between October 2010 and March 2012, the use of oral anticancer drugs was assessed by means of a telephonic pill count, a questionnaire and a review of the patient's medical file and pharmacy medication records. Parameters collected were patients' demographics, treatment characteristics, beliefs and attitude towards disease and medicines, self-reported adherence, side effects, quality of life and satisfaction about information. Patients off treatment filled out a questionnaire about the reasons for discontinuation. Optimal adherence was defined as ≥ 95%–≤ 105%. *Results.* The mean adherence rate (AR) (n = 177) was 99.1% with 20.3% of patients having a sub-optimal AR (< 95%, > 105%) consisting both of under- and over-adherence. Multivariate analyses showed that being on a cyclic dosing regimen (rather than a continuous regimen), not living alone and being highly educated increased the chances of optimal adherence (ORs = 4.88, 4.59 and 2.53, respectively). In addition, optimal adherence was found to be less common in patients reporting treatment control (OR = 0.77). One third of 79 patients off treatment reported their experienced side effects as one of the reasons for discontinuation. *Discussion.* Although most patients are fully adherent to oral anticancer agents, there is a substantial number tending to non-adherence. Patients living alone and those on a continuous dosing regimen are most likely to adhere sub-optimally. Interventions to improve adherence should specifically address these patients and be tailored to the needs of the individual patient.

For decades, chemotherapy was predominantly administered intravenously (IV). During the last years a substantial and rapidly growing number of oral anticancer agents has been introduced [1]. Oral administration may improve quality of life by its convenience and ease of use and patients prefer oral administration provided efficacy is at least similar to that of IV treatment [2,3]. Pharmaco-economic studies have shown that oral medication is superior to in-hospital IV treatment with respect to costs [4,5]. However, with the oral administration of anticancer drugs treatment adherence has become an issue of concern [6].

Prescribers of anticancer drugs might assume that patients with severe diseases, like cancer, take their medication as prescribed [7,8]. However, recent studies have shown that adherence to anticancer drug treatment is a serious problem [6].

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Ruddy and co-workers have reported adherence and persistence rates with oral anticancer agents between 16% and 100% [6]. Adherence was measured with various methods over different periods in different populations and mainly addressed hormonal therapy in breast cancer or oral chemotherapy in hematological diseases. Non-adherence consists both of under- and over-adherence and both types may have serious consequences [7,9]. Using less medication than prescribed may result in a lack of efficacy, thereby causing increased healthcare costs. For example, in chronic myeloid leukemia (CML), non-adherence with the use of imatinib has been reported as the main reason for not obtaining a molecular response following achievement of a complete cytogenetic response [10]. In contrast, over-adherence can lead to increased toxicity. Nilsson and co-workers have described that 30% of patients had an oversupply of their cancer medication (refill adherence $>120\%$) [8]. Over-adherence with capecitabine was even observed in a clinical trial population where patients were more closely observed than in daily practice. Three types of over-medication-errors can be distinguished: patients taking extra days of medication, patients taking extra doses per day and patients compensating for missed doses on a previous day [11].

The aim of the present study was to obtain more insight into the use of oral anticancer agents in daily practice. Adherence to oral anticancer drug treatment has not extensively been studied in patients and little is known about the factors influencing adherence. The results may lead to the development of specific interventions aimed at improved adherence.

Material and methods

Study design

We conducted an observational, multicenter study to assess adherence to treatment with oral anticancer agents (capecitabine, dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, lenalidomide, nilotinib, sorafenib, sunitinib, temozolomide and thalidomide) and factors influencing adherence. Four Dutch academic medical centers participated: VU University Medical Center Amsterdam (VUmc), Leiden University Medical Center (LUMC), Radboud University Nijmegen Medical Center (UMC St. Radboud) and the University Medical Center Groningen (UMCG) in the period October 2010 – March 2012. Data were collected by means of a telephonic patient interview, a patient questionnaire, a review of the patient's medical file and pharmacy medication records. The study was approved by the Medical Ethics Review Board of VUmc.

Study population

Patients from the age of 18 years, who had filled at least one prescription for an oral anticancer agent over a three-month period, were extracted from the pharmacy databases of the outpatient pharmacies of the participating hospitals. The medical oncologist, the hematologist or the pulmonologist excluded patients who were deceased or who were too ill to participate. Patients who were unable to fill out questionnaires and patients with insufficient knowledge of the Dutch language were excluded. Both patients on treatment and patients off treatment were eligible for participation (Figure 1). Patients willing to participate had to sign the informed consent form.

Data collection

Telephonic patient interview. Patients were contacted unannounced by the researcher by phone for a pill count. The count was performed using a standardized interview protocol. The patient counted the number of remaining pills. If the patient had returned an unknown number of pills to the pharmacy, a pill count could not be performed.

Review of the patient's medical file. Information on the prescribed number of pills, including dose, dose adjustments, (temporary) discontinuation or any other deviation from the prescribed treatment was retrieved from the patient's medical file. Information on disease and treatment plan, including cancer type, status of use, dosing regimen and duration of use was also obtained from the patient's medical file.

Pharmacy medication records. The total number of pills, dose in milligram (mg) and dosing regimen of oral anticancer agents were collected from the outpatient pharmacy of the hospital and any other visited local pharmacy. The total amount of drug was expressed in mg calculated on the basis of medication records of these pharmacies.

Patient questionnaires. Data on the patients' demographics, patients' attitude towards the disease and medicines and the patients' experiences with the use of oral anticancer agents were obtained using a questionnaire containing questions on demographics, disease and treatment. Both patients on treatment and patients off treatment were asked to fill out the Illness Perception Questionnaire (Brief IPQ) and the Beliefs about Medicines Questionnaire (BMQ). Patients on treatment were also asked to fill out the Medication Adherence Rating Scale (MARS), the European Organization for Research and Treatment of Cancer

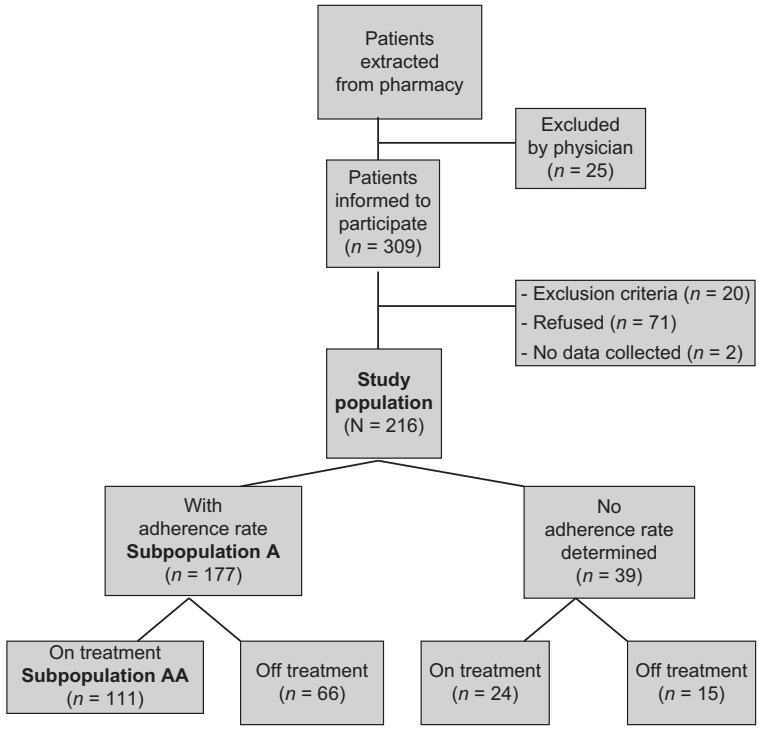

Figure 1. Flow chart of patients and exclusions used to obtain the Study Population and Subpopulations A and AA.

Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the Satisfaction with Information about Medicines Scale (SIMS) and the side effects questionnaire. Patients off treatment were asked to fill out questions about reasons for discontinuation.

The MARS, EORTC QLQ-C30, Brief IPQ, BMQ and SIMS questionnaires are described in brief below.

The MARS questionnaire has been validated to measure adherence and is used to obtain insight into adherence behavior [12]. MARS includes five questions, scored on a five-point Likert scale with a total score between 5 and 25. In our study, optimal adherent was defined as a score of 25 and all scores below 25 were considered sub-optimally adherent.

The EORTC QLQ-C30 version 3.0 is used to measure the quality of life (QoL) [13]. The 30 items-questionnaire, scored on a four-point scale, incorporates two questions about the global health status/QoL,15 questions which can be divided into five functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning), seven questions divided into three symptom scales (fatigue, nausea/vomiting and pain), five single items assessing additional symptoms commonly reported by cancer patients (dyspnea, insomnia, appetite loss, constipation and diarrhea) and one question about the financial impact of the disease. The scales and single item raw scores are transformed into a score ranging from 0 to 100. A higher score indicates a better quality of life.

The Brief IPQ is a nine-item questionnaire which is designed to rapidly assess the cognitive and emotional representations of illness [14]. Eight items are scored on a continuous linear scale from 0 to 10 to assess perceptions on the subscales consequences, time line, personal control, treatment control, identity, concern, coherence and emotional response. Item 9 is a casual item which was omitted in this study.

The BMQ gives insight into the attitude and beliefs of patients towards medication [15]. It consists of two five-item scales, the BMQ General and the BMQ Specific. The BMQ General can be subdivided into the BMQ General Harm which assesses the beliefs that medicines in general are harmful and the BMQ General Overuse which assesses the beliefs that medicines in general are overused by physicians. The BMQ Specific focuses on the medication that is prescribed for the patient's illness and can be subdivided into the BMQ Specific Necessity and BMQ Specific Concern. The BMQ Specific Necessity measures the patient's beliefs of the necessity of taking the medicine and the BMQ Specific Concern measures the patient's concerns about taking the medicine. The four subcategories of the BMQ are evaluated separately by calculating the scores to four total scores, ranging from 4 to 20 for BMQ General and 5 to 25 for BMQ Specific.

The BMQ necessity-concern differential is calculated from the two BMQ Specific scores.

The SIMS is a questionnaire measuring the satisfaction with the received information about the medicine and its use [12]. The SIMS consists of 17 questions addressing several issues concerning the results of treatment (effect, side-effects) in a five-item scale. If the patient indicates that "too much", "too little" or "no information" was provided, a score of zero is given. The answers "about right" and "not needed" are scored with one point. A total score is calculated by summing these scores and varies between 0 and 17. A higher score represents better satisfaction about the information received on the oral anticancer agent.

Adherence rate by means of pill count

The AR was expressed as the percentage of drug taken by the patient of the total amount prescribed and was calculated by means of the so-called Patient's files-Pharmacy records-Pill count method (PPP-method), which was developed for the present study. The total amount of drug prescribed was calculated on the basis of data collected from the patient's medical file. The total amount used by the patient was calculated by subtracting the amount in stock or returned to the pharmacy from the total amount collected from the pharmacy. All calculations were performed independently by two investigators.

Statistics

All analyses were performed using SPSS version 20.0 (SPSS inc. Chicago, IL, USA). Patient characteristics were summarized by their mean and standard deviation for continuous variables and by frequencies and percentages for categorical variables. The primary outcome variable was adherence, which was dichotomized with success defined as an AR $\geq$ 95%–$\leq$ 105%. Variables related to adherence were identified using logistic regression. All independent variables were first tested in univariate logistic regression analyses. Independent variables with a two-tailed p-value below 0.05 in the univariate analyses were included in a multivariate logistic regression analysis where forward selection was used to build the final model. Some categorical and continuous independent variables were dichotomized before analysis because of a large number of categories or of being highly skewed. Dichotomous independent variables included in the analyses were: cancer type (solid tumor vs. hematological malignancy), use status (on treatment vs. off treatment), education (low vs. high), living status (alone vs. together), paid work (yes vs. no), dosing regimen (continuous vs. cyclic), and MARS (25 vs. $<$25). All other independent variables (age, duration of use, SIMS, BMQ, IPQ, MARS total score, EORTC QLQ-C30) were included as continuous variables. The univariate and multivariate analyses were performed both in subpopulation A and subpopulation AA (Figure 1). Odds ratios (OR) together with their 95% confidence intervals (CI) and p-values were computed for the variables in the logistic regression models.

Results

Patients and characteristics

A total of 334 patients were extracted from the outpatient pharmacy information systems in four hospitals (Figure 1). Physicians excluded 25 patients. Of the 309 patients approached for participation, a total of 218 patients agreed on participation and signed the informed consent form. Reasons not to participate included insufficient knowledge of the Dutch language (n = 2), impossibility for researchers to get in contact (n = 12), patient died (n = 6), or unwillingness to participate for unknown reasons (n = 71). We excluded two patients who signed consent, but of whom we were not able to collect any data, resulting in a study population of 216 participants. Most patients (n = 135; 62.5%) were on treatment, 81 patients (37.5%) had discontinued treatment. For most patients (n = 177; 81.9%) it was possible to calculate the AR. These patients are referred to as subpopulation A. Reasons for absence of an AR were incomplete information from the physician, incomplete pharmacy medication records and patients being unable to count their pills. All patients within subpopulation A (with an AR) that were on treatment at the time of the study are referred to as subpopulation AA (n = 111; 51.4%).

Table I lists the characteristics of the patients of the total study population and the subpopulations A and AA. In the total study population, the mean age was 58.5 years and 55.6% was male. About two third of patients used an oral anticancer agent for the treatment of a solid tumor and 62.5% of the patients was on treatment at the time of the study. The patients used capecitabine (34.7%), lenalidomide (15.3%), imatinib (14.4%), temozolomide (11.6%), sunitinib (10.6%), thalidomide (5.1%), dasatinib (3.7%) and erlotinib and nilotinib (both 2.3%). There were no patients treated with everolimus, gefitinib, lapatinib or sorafenib. The characteristics of the subpopulations were similar to those of the total study population.

Adherence rate

Table II shows the AR as calculated for the subpopulations A and AA. The mean AR measured by

Table I. Characteristics of study population and subpopulations A and AA.

Characteristics	Study population N = 216		Subpopulation A: with adherence rate N = 177		Subpopulation AA: with adherence rate and on treatment N = 111	
	N	%	N	%	N	%
Age, years						
Mean	58.5		58.5		57.8	
Range	22–86		22–86		22–80	
Sex						
Male	120	55.6	100	56.5	63	56.8
Female	96	44.4	77	43.5	48	43.2
Hospital						
VUmc	55	25.5	45	25.4	31	27.9
LUMC	36	16.7	28	15.8	17	15.3
St Radboud	98	45.4	83	46.9	46	41.4
UMCG	27	12.5	21	11.9	17	15.3
Cancer type						
Solid tumor	143	66.2	121	68.4	65	58.6
Hematological malign	72	33.5	56	31.6	46	41.4
Unknown	1	0.5				
Oral anticancer agent*						
Capecitabine	75	34.7	64	36.2	26	23.4
Dasatinib	8	3.7	5	2.8	4	3.6
Erlotinib	5	2.3	3	1.7	3	2.7
Imatinib	31	14.4	26	14.7	23	20.7
Lenalidomide	33	15.3	27	15.3	19	17.1
Nilotinib	5	2.3	5	2.8	5	4.5
Sunitinib	23	10.6	17	9.6	10	9.0
Temozolomide	25	11.6	23	13.0	14	12.6
Thalidomide	11	5.1	7	4.0	7	6.3
Use status						
On Treatment	135	62.5	111	62.7	111	100.0
Off Treatment	81	37.5	66	36.3	0	0
Duration of use (days)						
Mean	373		375		408	
Range	26–3221		26–3221		26–3221	

	Duration of use (days) in subpopulation A (N = 177)			
	N	Mean ± SD	median	range
All agents*	176	374.6 ± 511.7	197	26–3221
Capecitabine	64	206.4 ± 191.5	154	28–1068
Dasatinib	5	606.0 ± 257.3	689	272–931
Erlotinib	3	391.3 ± 545.2	130	26–1018
Imatinib	26	949.2 ± 994.8	500	60–3221
Lenalidomide	26	291.8 ± 240.8	214	70–993
Nilotinib	5	153.0 ± 77.5	122	74–277
Sunitinib	17	505.1 ± 415.2	364	69–1594
Temozolomide	23	265.4 ± 265.6	256	35–1081
Thalidomide	7	142.4 ± 99.5	94	60–305

*No users of everolimus, gefitinib, lapatinib or sorafenib participated.

means of the PPP-method was 99.1% ± 5.4% with over one third of patients having an AR of exactly 100%. Thirty-six patients (20.3%) had an AR range < 95%–> 105% Most of these patients (63.9%) showed under-consumption.

Factors contributing to sub-optimal adherence

The results of the univariate analyses are shown in Table III. In subpopulation A, presence of the following factors was significantly associated with a higher chance of adhering optimally: high education (OR = 2.79), not living alone (OR = 3.51) and a cyclic dosing regimen (OR = 6.03). Presence of the following factors was negatively associated with the chance of optimal adherence: hematological cancer type (OR = 0.37), BMQ Specific Necessity (OR = 0.91) and IPQ-treatment control (OR = 0.78). In subpopulation AA (patients with AR and on treatment), presence of the following factors were positively associated with optimal adherence: high education (OR = 2.45), not living alone (OR = 8.77), patient-reported Hand-Foot Syndrome (OR = 1.63),

Table II. Adherence.

	Subpopulation A: with adherence rate N = 177		Subpopulation AA: with adherence rate and on treatment N = 111	
	N	%	N	%
Adherence				
Mean ± SD	99.1 ± 5.4		99.0 ± 5.4	
Range	80.4–121.4		81.4–120.8	
Adherence rate				
< 80	0	0	0	0
≥ 80–< 90	11	6.2	7	6.3
≥ 90–< 95	12	6.8	9	8.1
≥ 95–< 100	45	25.4	31	27.9
100	61	34.5	31	27.9
> 100–≤ 105	35	19.8	24	21.6
> 105–≤ 110	10	5.6	8	7.2
> 110–≤ 120	1	0.6	0	–
> 120	2	1.1	1	0.9
Adherence ≥ 95–≤ 105%				
Optimal	141	79.7	86	77.5
Sub-optimal	36	20.3	25	22.5
Adherence ≥ 90–≤ 110%				
Optimal	163	92.1	103	92.8
Sub-optimal	14	7.9	8	7.2

Adherence rate		mean	range
Capecitabine	64	98.8	80.4–109.7
Dasatinib	5	93.7	84.9–100.5
Erlotinib	3	91.3	85.2–98.5
Imatinib	26	98.7	81.4–121.4
Lenalidomide	27	99.6	88.0–108.3
Nilotinib	5	99.4	98.4–101.3
Sunitinib	17	101.8	96.3–111.4
Temozolomide	23	99.98	91.8–106.8
Thalidomide	7	98.1	81.4–107.7

SD, standard deviation.

Table III. Univariate analysis of variables associated with optimal adherence (≥95%, ≥105%).

	Subpopulation A: with adherence rate N = 177				Subpopulation AA: with adherence rate and on treatment N = 111			
	N	OR	95% CI	p-value	N	OR	95% CI	p-value
Sex (male gender)	177	0.63	0.30–1.30	0.211	111	0.63	0.26–1.55	0.317
Age	177	1.01	0.98–1.04	0.683	111	1.00	0.97–1.04	0.953
High education	173	2.79	1.22–6.37	0.015*	109	2.45	0.93–6.48	0.071
Not living alone	173	3.51	1.52–8.09	0.003*	109	8.77	3.01–25.58	<0.001*
Paid work	173	0.91	0.39–2.14	0.837	109	0.86	0.31–2.34	0.763
Hematological cancer type	177	0.37	0.17–0.78	0.009*	111	0.38	0.15–0.94	0.036*
Cyclic dosing regimen	177	6.03	2.75–13.26	<0.001*	111	9.23	3.13–27.25	<0.001*
Duration of use	176	1.00	1.00–1.00	0.537	111	1.00	1.00–1.00	0.990
SIMS	172	1.00	0.98–1.02	0.898	108	1.03	0.95–1.12	0.435
BMQ								
General overuse	170	0.92	0.81–1.05	0.215	107	0.89	0.76–1.04	0.145
General harm	172	0.89	0.77–1.03	0.129	108	0.89	0.74–1.06	0.191
Specific necessity	171	0.91	0.81–1.00	0.049*	107	0.90	0.79–1.02	0.086
Specific concern	170	0.97	0.88–1.07	0.523	107	0.96	0.85–1.08	0.459
Nec-conc differential	169	0.97	0.90–1.04	0.335	106	0.96	0.89–1.05	0.392
IPQ								
Consequences	169	1.10	0.94–1.28	0.235	107	1.10	0.92–1.33	0.289
Time line	166	1.04	0.93–1.18	0.486	105	0.98	0.81–1.19	0.844
Personal control	168	0.96	0.85–1.08	0.476	106	0.92	0.80–1.06	0.237
Treatment control	170	0.78	0.63–0.96	0.018*	107	0.85	0.65–1.12	0.246
Identity	170	1.10	0.98–1.25	0.118	107	1.08	0.94–1.26	0.283
Concern	171	1.03	0.89–1.18	0.698	108	1.12	0.95–1.33	0.175
Coherence	169	0.94	0.83–1.06	0.287	107	0.91	0.77–1.07	0.254
Emotional response	171	1.03	0.90–1.17	0.687	108	1.05	0.90–1.22	0.537
Patient reported side effects								
Fatigue					106	1.27	0.81–1.99	0.292
Hand foot syndrome					106	1.63	1.01–2.62	0.045*
Skin reactions					103	1.14	0.76–1.71	0.538
Diarrhea					105	1.24	0.74–2.06	0.414
Nausea					106	1.23	0.69–2.17	0.486
Stomach ache					105	1.59	0.74–3.40	0.234
Constipation					103	1.31	0.79–2.18	0.294
Infection					105	0.93	0.51–1.70	0.804
Headache					105	0.78	0.40–1.52	0.469
Muscle joint pain					104	1.17	0.76–1.81	0.486
Edema					104	0.64	0.44–0.94	0.024*
Mucositis					105	1.59	0.53–4.79	0.409
Weight loss					106	0.94	0.50–1.76	0.836
Cough					104	0.68	0.40–1.13	0.134
MARS								
MARS total score					105	2.15	0.95–4.85	0.067
MARS (25 vs. <25)					105	4.44	1.52–12.96	0.006*
EORTC QLQ-30								
Global health status					109	0.98	0.96–1.01	0.108
Functional scales								
Physical functioning					108	1.01	0.98–1.03	0.624
Role functioning					108	1.00	0.98–1.01	0.027*
Emotional functioning					109	1.00	0.98–1.03	0.713
Cognitive functioning					109	1.01	0.99–1.03	0.357
Social functioning					109	0.99	0.97–1.01	0.215
Symptom scales								
Fatigue					108	1.00	0.98–1.02	1.000
Nausea and vomiting					109	0.97	0.92–1.01	0.132
Pain					109	0.99	0.96–1.01	0.235
Dyspnea					109	1.01	0.99–1.02	0.607
Insomnia					109	1.02	1.00–1.03	0.061
Appetite loss					109	1.00	0.98–1.02	0.850
Constipation					109	0.99	0.97–1.01	0.483
Diarrhea					108	1.01	0.99–1.02	0.590
Financial difficulties					108	0.99	0.97–1.01	0.195

BMQ, Beliefs about Medicines Questionnaire; CI, confidence interval; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; IPQ, Illness Perception Questionnaire; MARS, Medication Adherence Rating Scale; OR, odds ratio; SIMS, satisfaction with Information about Medicines Scale. *significance ($p \leq 0.05$).

a cyclic dosing regimen (OR = 9.23) and a score of 25 on the MARS scale (OR = 4.44). Moreover, in subpopulation AA, negative associations were found between optimal adherence and hematological cancer type (OR = 0.38), patient-reported oedema (OR = 0.64) and EORTC QLQ-C30 Role functioning (OR = 0.98). Using stepwise logistic regression with forward selection we found models with four and two variables for subpopulation A and AA, respectively. Due to missing variables in subpopulation A, 168 of 177 patients and in subpopulation AA, 105 of 111 patients were included. The results are shown in Table IV. In subpopulation A, dosing regimen and living status had the highest OR, respectively 4.88 and 4.59. These factors were considerably higher in subpopulation AA; not living alone [OR = 20.69, 20 patients (18.3%) living alone and 89 patients (81.7%) not living alone] and cyclic dosing regimen [OR = 21.10, 65 patients (58.6% with a cyclic dosing regimen and 46 patients (41.4%) with a continuous dosing regimen], but confidence intervals are also very broad. The factors IPQ treatment control (OR = 0.77) and high education (OR = 2.53) were significantly associated with optimal adherence in subpopulation A only.

Discontinuation

Of the 81 patients who had discontinued the use of an oral anticancer agent, 79 patients (97.5%) filled out the questions about discontinuation (Table V). Discontinuation of medication was reported by 43.0% of the patients because of completion of treatment. One third of the patients (34.2%) reported side effects as one of the reasons for discontinuation and 11 patients (13.9%) had discontinued the use because of ineffectiveness. Most patients (88.6%) discontinued on the initiative of their physician.

Table IV. Multivariate analysis of variables associated with optimal adherence (≥95%, ≤105%).

	Subpopulation A: with adherence rate		
N = 168	OR	95% CI	p-value
Cyclic dosing regimen	4.88	2.02–11.77	<0.001*
Not living alone	4.59	1.68–12.52	0.003*
IPQ treatment control	0.77	0.61–0.98	0.036*
High education	2.53	1.00–6.41	0.050
	Subpopulation AA: with adherence rate and on treatment		
N = 105	OR	95% CI	p–value
Cyclic dosing regimen	21.10	4.46–99.88	<0.001*
Not living alone	20.69	4.06–105.43	<0.001*

CI, confidence interval; IPQ, Illness Perception Questionnaire; OR, odds ratio. *significance (p ≤ 0.05).

Table V. Questionnaire on discontinuation.

(N = 79)	N	%
Reasons for discontinuation*		
Side effects	27	34.2
Lack of efficacy	11	13.9
Scheduled	34	43.0
Other	22	27.8
Initiative for discontinuation		
Patient	6	7.6
Physician	70	88.6
Partner/family	1	1.3
Other	2	2.5
Experience		
Positive	27	34.6
Neutral	30	38.5
Negative	21	26.9
Don't know	1	

*more than one reason possible.

Discussion

The majority of patients using oral anticancer agents has a high AR (mean AR 99.1% ± 5.4%). Although the mean adherence is high, there is a considerable number of patients (20.3%) that tends to non-adherence. There is a lack of consensus on the minimum and maximum AR to distinguish adherence from non-adherence [6,16]. Ideally, the threshold of optimal adherence should be based upon clinical relevance. However, only limited data on the clinically relevant minimum intake of a specific drug that is necessary to provide the expected effect is available. Frequently used cut-off points for non-adherence range from 80% to 95% [6,16]. In chronic diseases an AR of 80–120% is often quoted as acceptable. However, among patients with serious conditions, an AR of 95% is often considered mandatory as consequences of both reduced efficacy and toxicity can be serious [16,17]. We used the range of ≥95%–≤105% to define optimal adherence as it provides best insight into possible risk factors that may lead to sub-optimal adherence.

Adherence with the use of oral anticancer agents has been studied previously. Similar to our results, non-adherence with capecitabine has been found in 20–25% of patients [17–19]. Other research on adherence focuses on CML. One third of patients appeared non-adherent with imatinib [12], with ARs ranging from 24% to 202% of prescribed dose [10]. This is of particular interest, because the consequences of non-adherence to imatinib in CML treatment was studied. When adherence was ≤90% no complete molecular response was seen [10]. In our study with several oral anticancer agents, we found ARs tending to under-adherence (13.0% with AR < 95%), as well as to over-adherence (7.3% with AR > 105%). The issue of over-adherence in oncology has also been addressed by other investigators [6,11].

The type of dosing regimen was the most important predictive factor for sub-optimal adherence. Patients using their medication in a cyclic dosing regimen (periods of daily use alternated with stop periods) were more likely to be optimally adherent than patients using their medication continuously (either once or twice daily). In a systematic review the relationship between adherence and the prescribed number of doses per day has been analyzed [20]. Simpler, less frequent dosing usually resulted in higher adherence as reported for various types of medicines [20]. In CML, however, comparing dasatinib once daily with nilotinib twice a day and separated from food intake, has shown dasatinib patients to be less adherent [13% lower percentage days covered (PDC)] [21]. To our knowledge, the influence of a complex cyclic dosing regimen, as often used in oncology, on adherence has not been studied previously. Though cyclic dosing regimens are more complex than continuous use, adherence to these schedules is better than to regimens requiring continuous intake on a daily basis. Apparently, forgetting to take the pills is more likely to occur in a regular continuous dosing regimen than in a complex regimen requiring full attention.

The living status of patients was also related to adherence. Patients living with a partner, children or someone else were more likely to take their pills. This finding is consistent with previous adherence studies. Greater social support is an independent predictor of optimal adherence to imatinib in CML [22]. In other patient groups, perceiving social support was also associated with a higher adherence [23]. Living alone has shown to be a factor in Swedish oncologists' decision-making [24]. Oncologists tailor treatment in patients living alone to avoid side effects. This method could also be beneficial to enhance adherence.

In the multivariate analyses of sub-population A, the level of education and IPQ-treatment control were also related to adherence. In another study, educational status was not a predictor for non-adherence [25]. In a review exploring illness perceptions in mental health, adherence was linked to beliefs that treatment could control one's illness [26]. Our results show the opposite; patients trusting the effect of their treatment were more likely to be sub-optimally adherent. There is no clear explanation for these contrasting findings. In the univariate analyses, the type of cancer had a substantial effect on adherence (OR 0.38). Patients with a hematological malignancy were more likely to be sub-optimally adherent than patients with a solid tumor. However, in the multivariate analyses this effect disappeared. The number of patients in our study was too small to determine whether this was due to confounding by dosing regimen.

Patient's experiences with the use of oral anticancer agents in daily practice and reasons for discontinuation of treatment have not been studied previously. About one third of the patients reported side effects as one of the reasons for discontinuation. Unfortunately, it is not known whether this perspective of the patient matches with the reason for discontinuation according to their physician. While most patients reported not to discontinue treatment on their own initiative, physicians have good opportunity to address patients' side effects.

There are some strengths and limitations to discuss. To our knowledge, assessment of the AR of treatment with erlotinib, lenalidomide, sunitinib, temozolomide and thalidomide are unique. We performed this study in four centers and included a large number of patients. The pill count method (the PPP-method), which was developed fot the present study is an accurate method is an accurate method to determine adherence to agents which are used in complex cyclic dosing regimens and dosing which are often subject to adjustments by the physician. The PPP-method combines the result of an unannounced telephonic pill count with information from the patient's medical file. By studying the patient's file, adjustments made by the physician like shortening a course, lowering a dose or temporary discontinuation, were not incorrectly interpreted as non-adherence. In univariate logistic regression, we found a significant positive association between our outcome measure (optimal adherence measured with the PPP-method) and the self-reported adherence measured by means of the MARS questionnaire. The relationship between adherence behavior measured with both methods reinforces the reliability of the data. Further research on validation of this pill count method is needed to prove its value in adherence research. Another strength of this study is the wide range of factors explored to determine which patients are at risk of non-adherence. Unfortunately, it was impossible to precisely estimate the extent of the influence of all factors related to sub-optimal adherence. More patients are required to estimate the odds ratios in a more accurate way. Furthermore, cohort studies aimed at a specific agent are needed to confirm our findings. We combined analyses of a large number of oral anticancer agents used in different stages of malignancies of various treatment durations. Though not very specific, this method offered a good opportunity to widely explore factors related to suboptimal adherence in oncology.

In conclusion, although most patients are fully adherent, a considerable number of patients tends to non-adherence, consisting of both under- and over-adherence. Patients living alone and using their oral anticancer agent in a continuous dosing regimen

are most likely to adhere sub-optimally to their prescribed regimens. Interventions to enhance adherence should specifically be aimed at patients at risk for non-adherence and should be tailored to the needs of the individual patient.

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