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Research Article

Analysis of Medication Status of Subjects in Oral Anticancer Drug Clinical Trials and Discussion on Countermeasures

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Abstract

Objective: The present study aimed to understand the medication status of subjects participating in oral anticancer drug clinical trials, analyze the issues and influencing factors during the medication process, and propose better management approaches for subsequent clinical trials.

Methods: The study included subjects enrolled in oral anticancer drug clinical trials conducted in a cancer hospital in China from 2010 to 2022. We collected general information of the included subjects and the trials and reviewed the distribution and return documentation as well as diary cards of the subjects' medications. Specific issues occurring during the medication process were analyzed, and the subjects' medication compliance was estimated. The chi-square test or Pearson's correlation analysis was performed on medication information, subjects' basic information, and specific issues encountered by the subjects. Linear regression was used for attribution analysis of specific issues encountered by the subjects during the medication process.

Results: Thirty-two clinical trials on oral anticancer drugs conducted between 2010 and 2022 and involving 700 subjects were reviewed. Among these, 217 subjects experienced loss of medicine, missing dose, overdose, or nonreturn of trial drugs during the medication process in the clinical trial. A total of 93.2% of the medication cycles had 80–120% compliance. Multiple linear regression analysis revealed that sex, number of medication cycles, trial initiation time, and different types of trial drugs were the factors that affected the number of medication issues encountered by the subjects.

Conclusions: Approximately one-third of the subjects participating in oral anticancer drug clinical trials experienced loss of medicine, missing dose, or overdose during the medication process, and the medication issues varied across the different medication periods. The medication compliance of the subjects was good; however, there were still issues such as missed medication during the medication process. Targeted evaluation and monitoring approaches should be established for different experimental categories, subject gender, and medication duration, and effective management measures should be introduced to minimize medication issues during drug clinical trials.

Keywords: Oral Therapy; Anticancer Clinical Trial; Subjects; Medication Status; Countermeasures.

INTRODUCTION

With the increase in cancer incidence and the acceleration of new drug development in China, an increasing number of novel anticancer drugs have entered the clinical trial stage. Cancer treatment has evolved from chemotherapy and radiotherapy to targeted therapy, immunotherapy, and multimodal therapy. In a clinical trial, participants are required to take medicines correctly to comply with the established protocol, and the investigated drugs are distributed and recycled through a closed-loop management system; these are prerequisites to ensure comprehensive and accurate collection of the data related to the efficacy, adverse reactions, and pharmacokinetics of the investigated drugs. The "Good Manufacturing Practices for Drug Products" released by the China Food and Drug Administration clearly states that the distribution, use, and return of trial drugs must be balanced [1], and the related documentation should strictly comply with these requirements. Previous clinical trials mostly used standardized scales to investigate the compliance of patients. Following the emergence of oral anticancer targeted drugs, surveys of compliance with oral targeted drugs have gradually emerged [2,3]. Since the launch of the first domestic PD-1 inhibitor in 2018 in China [4], several clinical trials for combinational treatments including immunotherapy have been conducted; however, few studies have investigated the issues arising during the clinical trials of oral drugs, such as patient compliance with treatment regimens. The present study aimed to analyze this aspect by enrolling subjects in clinical trials of either a single oral anticancer agent or combinational treatments. By conducting a thorough examination of the subjects' medication diary cards as well as distribution and return records, this study intended to determine the specific challenges encountered during clinical trials by analyzing and quantifying patients' compliance, which could enhance patient management strategies and improve the quality of clinical trials.

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MATERIALS AND METHODS

Data Collection

We collected drug administration information from oral anticancer drug clinical trials conducted in a cancer hospital in Beijing, China, from January 2010 to July 2022. And all the clinical trials mentioned have been approved by the Medical Ethics Committee of Beijing Cancer Hospital, and have received informed consent and permission from the participants for data analysis. The following information was collected: (1) basic information of the subjects, such as sex, age, and trial items; (2) issues occurring during the medication process and subjects' compliance; and (3) basic information of the trials, such as types of trial drugs (oral medication or oral medication combined with intravenous medication) and trial initiation time.

METHODS

Classification of Medication Issues and Evaluation of Compliance: By reviewing the subjects' medication diary cards, the issues that occurred during the medication process were classified as follows: (1) loss, including loss of trial medicines, aluminum foils, packaging bottles, or boxes; (2) missing dose; (3) overdose; (4) nonreturn of trial drugs; (5) loss and missing dose; (6) missing dose and overdose; (7) loss, missing dose, and overdose; and (8) others such as damage of the packaging material or more or less quantity of returned drugs or complaints of subjects that they did not miss or took extra doses.

We examined the distribution and return documentation of the trial drugs, recorded the number of medication cycles for each subject, reviewed the medication diary cards, and documented the number of cycles where the returned drug quantity showed discrepancy; by using these details, we calculated the medication compliance based on the cycles in which missing dose or overdose occurred. The calculation of medication compliance adhered to the standard approach outlined in most clinical trial protocols, where compliance was determined using the formula: actual medication dosage/planned medication dosage × 100%. Based on this formula, if the compliance was < 80% or > 120% (excluding suspensions and protocol-mandated dose adjustments), the subjects were considered noncompliant.

Data Entry and Analysis: SPSS version 22.0 software was used for data entry and statistical analysis. The general information of the subjects; number of medication cycles; number of problematic cycles; occurring issues; corresponding time point (first cycle, mid of the medication cycles, and last cycle); and essential information of trials, including types of trial drugs and trial initiation time, were inputted into SPSS. Sex, age, occurring issues, time points, and types of trial drugs were classified and assigned the corresponding values. Descriptive statistical analysis was performed on both categorical and continuous data. Count data were expressed as percentage (%), and continuous data were expressed as $\bar{x} \pm s$. Pearson's correlation coefficient was used for correlation analysis, and the chi-square test was used for inter-group comparisons. The chi-square test or Pearson's correlation analysis was performed on the subjects' basic information, medication details, and occurring issues. Multivariate analysis was performed using binary logistic regression and multivariate linear regression methods to investigate the association of various categorical and continuous variables with the occurrence of medication issues (yes or no) or the number of problematic cycles. $P < 0.05$ was considered statistically significant.

RESULTS

General Information of the Included Trials and Study Subjects

The study included 32 clinical trials of oral anticancer drugs that were conducted between 2010 and 2022 and involved 700 subjects (375 males [53.6%] and 325 females [46.4%]). The average age of the subjects was 55.42 ± 11.92 years (range: 11–86 years). Regarding the age of the subjects, 213 (30.4%), 233 (33.3%), and 195 (27.9%) subjects were in the age groups of ≤ 50, 51–60, and 61–70 years, respectively. Among the 32 clinical trials, 4 trials were initiated before 2015, and an average of 5 trials were conducted annually from 2016 to 2021. Eighteen trials focused solely on oral drug administration, while 9 trials involved a combination of oral and intravenous drug administration (Table 1).

Table 1: General information of the trials.

Items		Number	Percentage (%)
Trial initiation time	2010–2015	4	12.5
	2016	4	12.5
	2017	5	15.6
	2018	4	12.5
	2019	4	12.5
	2020	6	18.8
	2021	5	15.6
Type of trial drugs	One oral medicine	18	56.2
	Two oral medicines	5	15.6
	Oral + intravenous medicines	9	28.1

Drug Administration and Compliance of the Subjects

Of the 700 subjects, 248 (35.4%), 205 (29.3%), 139 (19.9%), and 108 (15.4%) subjects received 1–5, 6–10, 11–20, and > 20 cycles of drug administration, respectively. The minimum and maximum number of cycles was 1 and 87, respectively. A total of 217 subjects (31.0%) showed discrepancies in returned trial drugs and diary card records, which were primarily attributed to loss of medicine (74 subjects, 10.6%) and missed doses (62 subjects, 8.9%). In 142 subjects (20.3%), this discrepancy frequently occurred in only 1 cycle. Compliance was determined by analyzing 190 cycles in 120 subjects who experienced missing dose or overdose situations. In 177 cycles (93.2%), compliance ranged from 80% to 120% (Table 2).

Moreover, among the three time points, 34.6% and 49.0% of drug loss occurred in the first cycle and mid of the medication cycles, respectively. Additionally, 69.0% of missed dose issues and 67.7% of overdose issues also occurred in the mid of the medication cycles. In contrast, not returning drugs in the last cycle was an issue in 75.9% subjects (Table 3).

Univariate Analysis of Medication Issues of the Subjects

A univariate analysis was conducted with age, sex, number of medication cycles, type of trial drugs, trial initiation time, and trial items

Table 2: General information of drug administration (n = 700 subjects).

Items	Group	Number	Percentage (%)	Items	Number	Percentage (%)
Number of cycles	01-May	248	35.4	Loss	74	10.6
	06-Oct	205	29.3	Missing dose	62	8.9
	Nov-20	139	19.9	Overdose	13	1.9
	> 20	108	15.4	Nonreturn	19	2.7
Discrepancy between drug return and medication card	No	483	69	Loss and missing dose	22	3.1
	Yes	217	31	Missing dose and overdose	9	1.3
Number of problematic cycles	0	483	69	Loss, missing dose, and overdose	4	0.6
	1	142	20.3	Others	13	6.7
	2	42	6	< 80%	10	5.3
	3	18	2.6	> 120%	3	1.6
	> 3	15	2.2	80–120%	177	93.2

as the factors. The results showed that the number of medication cycles, type of trial drugs, and trial items were significantly associated with the occurrence of medication issues and the number of problematic cycles. Sex was associated only with the number of problematic cycles, while age and the trial initiation time were associated with trial items (Table 4)

Multivariate Analysis of Medication Issues of the Subjects

A multivariate analysis was conducted using the occurrence of medication issues (yes or no) or the number of problematic cycles as dependent variables and age, sex, number of medication cycles, type of trial medications (oral medicines or oral medicines combined with intravenous medicines), trial initiation time, and trial items as independent variables. Binary logistic regression or multivariable linear regression was used to identify the independent factors that contributed to the medication issues of the subjects. The number of medication cycles, type of trial medications, and specific trial items were associated with the occurrence of medication issues (Table 5), while sex, number of medication cycles, trial initiation time, and specific trial items were associated with the number of problematic cycles (Table 6).

Table 3: Issues in various time intervals.

Items	Intervals	Number	Percentage (%)	Items	Intervals	Number	Percentage (%)
Loss	First cycle	36	34.6	**Overdose**	First cycle	5	16.1
	Mid of the cycles	51	49		Mid of the cycles	21	67.7
	Last cycle	11	10.6		Last cycle	2	6.5
	Others	6	5.8		Others	3	9.7
Missing dose	First cycle	15	15	**Nonreturn**	First cycle	5	17.2
	Mid of the cycles	69	69		Mid of the cycles	1	3.4
	Last cycle	10	10		Last cycle	22	75.9
	Others	6	6		Others	1	3.4

Table 4: Factors associated with medication issues according to univariate analysis

	Number of problematic cycles			Occurrence of specific issues		
	Pearson's correlation	Chi-square	P-value	Pearson's Correlation	Chi-square	P-value
Sex	-	15.582	0.029	-	12.853	0.538
Age	-0.005	-	0.888	0.081	-	0.032
Number of cycles	0.237	-	0	0.162	-	0
Type of trial drugs	-	58.87	0	-	1.087	0
Trial initiation time	-0.068	-	0.072	-0.136	-	0
Trial items	-	3.443	0	-	7.126	0

Table 5: Factors associated with the occurrence of medication issues according to binary logistic regression analysis.

Factors	Sig	Exp(B)	95% confidence interval for Exp(B)	
			Lower	Upper
Sex	0.17	1.262	0.905	1.759
Age	0.73	0.969	0.812	1.157
Number of medication cycles	0.003	1.021	1.007	1.035
Type of trial medicines	0.008	1.348	1.079	1.684
Trial initiation time	0.299	1.098	0.92	1.31
Trial items	0.01	0.936	0.89	0.984

Table 6: Factors associated with the number of problematic cycles according to multivariate linear regression analysis.

Factors	t	Sig
Sex	2.384	0.005
Age	0.0449	0.654
Number of medication cycles	5.124	0
Type of trial medicines	1.415	0.157
Trial initiation time	2.153	0.032
Trial items	-3.257	0.001

DISCUSSION

Issues of Drug Loss, Missing Dose, and Overdose Occurred in 30% of the Subjects

We reviewed the medication records of the 700 subjects and found that the issues of drug loss, missing dose, and overdose occurred in 217 (nearly 30%) subjects. Among these 217 subjects, 75 (34.6%) subjects had issues of missing dose and overdose, i.e., change of compliance. Previous studies predominantly used a compliance scale to assess compliance to oral chemotherapeutic drugs [2,3] and to determine compliance and the influencing factors during the follow-up [5-7]; however, data regarding the specific issues that occurred in the medication process during a clinical trial are limited.

Diverse Issues Arising During Clinical Trials

Drug loss issue primarily occurred in the first medication cycle and mid of the medication cycles; for instance, loss of aluminum foils, packages, and bottles often occurred in the first cycle, while loss of drug pills mostly occurred in the mid of the medication cycles. Missing dose and overdose often occurred in the mid of the medication cycles, and the issue of nonreturn of drugs mostly occurred in the last cycle probably because subjects stopped their visit in the last cycle due to death or serious adverse events.

Our study revealed significant associations between sex, total number of medication cycles, trial items, type of trial medicines, and number of problematic cycles. Females had more issues during drug administration in clinical trials; moreover, the longer the medication cycles, the higher was the likelihood of developing medication issues. Age and trial initiation time were associated with medication issues. The older subjects experienced a higher incidence of medication issues. Although fewer trials were initiated during 2010–2015, there was no proportional decrease in the number of medication issues. These results agreed with findings from other studies, which demonstrated that a longer chemotherapy duration is associated with poor patient compliance [8]. Additionally, longitudinal studies indicate that noncompliance with oral chemotherapeutic drugs has been a consistent issue over time [9]. Hence, it is imperative to establish a robust and trusting communication relationship among researchers, research nurses, clinical trial coordinators, and participants. Newly enrolled subjects must be fully informed about the usage of trial drugs and the potential consequences. Beyond the details of adverse reactions, subjects should also receive information about the trial's management protocols for the drugs. This includes guidance on whether to retain the used trial drug package, instructions on maintaining the medication diary card, and clear stipulations on the card for easy reference by subjects. For participants undergoing long-term follow-up, it is crucial to stress the importance of avoiding abrupt discontinuation of the medication or taking repeated doses due to uncertainty, as this could lead to increased adverse reactions. In the case of any discomfort, patients should promptly notify the investigator or clinical trial coordinator for appropriate intervention. To enhance the accuracy of the medication records of the subjects, relevant forms for medication distribution and drug recovery should comprehensively document specific medication details in each cycle, including instances of missed doses and excess medication, along with occurrence dates. For specific trials, it could be beneficial to consider the utilization of the transtheoretical model to predict the medication compliance of the subjects and educate them accordingly. Researchers such as Arafat Y and Platt I successfully used the transtheoretical model to forecast medication compliance of the subjects and design targeted interventions at specific stages, thereby yielding positive outcomes [10,11].

Binary logistic regression analysis indicated that the number of medication cycles, type of trial medicines, and trial items were the factors that influenced whether a subject experienced medication issues. Moreover, sex, number of drugs, and trial initiation time were the statistically significant factors that affected the number of cycles in which the subjects encountered medication issues. The number of anticancer drug clinical trials in China has remarkably increased after 2016 [12]. The trajectory of anticancer drug clinical trials in China has progressed through distinct stages, transitioning from the exploratory stage (1959–1977) to the preliminary standardization stage (1977–1994), the standardized management stage (1995–2015), and the robust development stage since then [13]. This evolution aligns with the enactment and enforcement of the new version of Good Clinical Practice (GCP) in 2020 [14], thereby contributing to increased awareness and reinforced detailed management of clinical trials, which may explain the association between the trial initiation time and the number of problematic cycles.

Various Medication Issues Need to be Improved Despite Good Compliance

In our study, the issue of missing dose or overdose occurred in 120 subjects and 190 medication cycles. Notably, 93.2% of the medication cycles exhibited compliance levels in the range of 80–120%, thus meeting

the protocol requirements. The inclusion of these subjects did not compromise the data analysis. However, for individuals with medication compliance below 80% or above 120%, their potential inclusion in the analysis will depend on specific circumstances. The overall medication compliance of the subjects in our study was remarkable; it showed consistency with, yet deviation from, findings of both domestic and foreign studies. Foreign studies reported a broad spectrum of patient medication compliance, ranging from 20% to 100% [15], with complete compliance rates varying between 14.2% and 57.4% [16,17]. Disparities in medication compliance also exist among patients with different types of tumors. Interestingly, a high incidence rate of 14.8–44% is noted for over-compliance, wherein patients exceed the prescribed drug dosage [16,18]. In China, substantial variations have been reported in medication compliance for oral anticancer drugs. For instance, Yang Yusi et al. evaluated the compliance of patients for oral capecitabine and found an overall good compliance [2]. In contrast, Zhang Xinge et al. investigated compliance among breast cancer patients and reported overall poor compliance [3]. These variations may be attributed to differences in tumor types, distinct adverse drug reactions, and the different statistical methods used to assess compliance.

To ensure subjects' compliance, some researchers have used strategies such as leveraging the social support system and sending email or text message reminders prior to scheduled administration to enhance compliance. Interestingly, the utilization of social support, such as finding a companion, did not yield a substantial improvement in the medication compliance of the subjects. In contrast, the incorporation of automatic reminder functions, such as email and text message alerts, significantly enhanced subjects' compliance [19]. Other studies have investigated the use of distinct pill boxes or 3D-printed pill dispensers tailored for individual subjects to strengthen medication compliance [20]. With the increasing utility of artificial intelligence and the internet in the healthcare sector, applications and smart devices designed for clinical trial medication management can be used to remind subjects about their administration schedules and provide pertinent information on medication precautions.

CONCLUSIONS

During drug clinical trials, it is essential to ensure accurate medication administration to the involved subjects and to implement a closed-loop management system for experimental drugs. The present study reviewed medication records of 700 subjects who participated in clinical trials for oral anticancer drugs spanning from 2010 to 2022 to analyze their current medication status. Based on the findings, the study proposes the implementation of appropriate assessment and oversight measures tailored to diverse types of trial drugs, subject sex, and administration duration as well as to improve the quality of documentation, enhance subjects' compliance through different strategies, and introduce intelligent management measures to minimize the occurrence of medication-related issues. It is important to note that the study subjects came from a single cancer hospital in Beijing. Therefore, future studies should expand the scope of research by conducting multicenter investigations and analyzing additional factors that influence the medication use of subjects to provide a more comprehensive evidence base for improving clinical trial outcomes.

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