

Adherence to Oral Targeted Anti-Lung Cancer Therapy: A Qualitative Interview Study

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Objective: Oral targeted antineoplastic drugs (OTADs) are becoming more and more acceptable for lung cancer treatment due to their advantages such as the convenience of administration and milder side effects. However, medication adherence represents a major issue for prolonged OTAD treatment. In this study, the factors associated with treatment adherence to OTAD were explored through the Adherence Influencing Factor Framework suggested by WHO. Based on these results, we further examined the potential factors related to social psychological cognition in OTAD adherence in patients with lung cancer.

Methods: This qualitative study was conducted in public hospitals in Henan, China. Data were collected through semi-structured interviews with selected lung cancer patients. Face-to-face interviews were audio-recorded and transcribed for thematic analysis.

Results: Of the 21 patients interviewed, 17 were males and 4 were females. The analysis of the data led to four themes, ie, patient-related factors (medication-taking introspection, family structure, weigh the pros and cons of OTAD treatment), medication-related factors (medication experience, adverse reactions, information access), physician/nurse-related factors (shared decision making, doctor's reaction, nurse's inquiry) and society-related factors (fear, stigma).

Conclusion: Family structure, weigh the pros and cons of OTAD treatment, information access, shared decision making, nurse's inquiry are potential factors affecting OTAD adherence in lung cancer patients. Providing drug information support to patients, inviting patients to join in shared decision-making and strengthening doctor-patient-nurse cooperation are important for improving medication adherence. Further research should be conducted to help healthcare providers to promote the medication adherence of lung cancer patients to OTAD treatment.

Keywords: OTAD adherence, qualitative study, lung cancer, targeted cancer therapy

Introduction

As one of the most common and deadly cancers, lung cancer is responsible for about 2 million deaths per year worldwide.¹ In recent years, oral antineoplastic agents (OAAs) have increasingly become a primary form of lung cancer treatment due to their convenience, enhanced safety profile (eg, fewer clinical visits, easier administration) and minimized resource use (eg, storage, demand from the infusion centers).^{2,3} As one of the most popular forms of OAAs, oral targeted antineoplastic drug (OTAD), displays great advantages in terms of overall survival (OS), progression-free survival (PFS), response rate (RR) and adverse reactions.⁴⁻⁶ Nevertheless, the widespread application of OTAD also poses the problem of medication adherence to the care of cancer patients, especially when a long-term treatment is required. This is because different from the controlled, in-clinic drug administration

monitored by care teams (eg, oncologists, nurses, pharmacists), OTADs are generally applied by patients at home, and direct supervisions are not available.³

Medication adherence is defined as the extent to which a patient follows the treatment regimen that is recommended by prescribers.⁷ Medication adherence includes two main components: 1) medication implementation, ie, taking the right drug at the right dose on time; 2) medication persistence, ie, the time duration between initiation and discontinuation of treatment. As demonstrated by multiple studies, poor medication adherence could result in compromised therapeutic efficacy, reduction in disease-free survival, prolonged hospitalization, increased burden for both patients and caregivers, disease progression, and even death.^{8,9} When it comes to targeted cancer therapy, good medication adherence is especially important, as small deviations from the treatment regimens may result in drug resistance and treatment failure.¹⁰ Although it is normally expected that cancer patients should display better adherence to their treatment given their life-threatening illness, it has been proven that adherence should never be assumed, even in oncology.¹¹

While patients with lung cancer normally display higher motivation towards appropriate OTAD application, challenges remain. According to a survey, 53% of lung cancer patients forgot oral targeted medicines at least once in 2 weeks.¹² In another case, Timmers investigated lung patients undergoing erlotinib treatment and found that more than 30% patients recorded a compromised compliance rate (<95%), and during the one-month investigation, 21% patients failed to correctly take the medicine (in terms of dose and administration time).¹³

Previous researches have shown that proper self-management of side effects, choosing drugs based on family economic conditions, age, and severity of disease all related to medication adherence.^{14–16} However, these findings were all developed from the perspective of physicians, some important factors of medication adherence such as patients' perspectives about drug administration, family structure were generally overlooked. Drug adherence is a complex dynamic process of individual behavior, determined by multiple factors including treatment scheme, patients (eg, economic burden, cognitive ability, therapeutic attitude), and health-care providers (eg, doctors/nurses' reactions to therapy, society's perception of anticancer drug treatment). As many of these factors are difficult to be accurately quantified, it is not practical to simply use quantitative study when this topic is investigated. Taking this into account, a qualitative study was used in this study. As qualitative study can not only provide insights into the process of drug adherence (to study the context of an experiential process), but also provide a unique opportunity to understand clinical issues from a patient's perspective.

Previous qualitative interviews typically focused on predetermined factors, which made it difficult to detect in-depth influence factors and prevent new information from being identified.^{17,18} Here, via using the Adherence Influencing Factor Framework, for the first time, we systematically explored the influence factors of OTAD adherence from the perspective of patients and examined the social-psychological activities of patients with lung cancer regarding medication adherence.

The results of this study can be used for optimizing the current caring scheme of lung cancer patients with OTAD treatment. And importantly, given the increased application of OTAD in different types of cancers, this work may also contribute to the clinical management of OTAD treatment to other types of cancers.

Methods

In this work, the influence factors of medication adherence of lung cancer patients were identified via a qualitative exploratory descriptive study utilizing conventional content analysis. The interview is featured by a semi-structural style in line with the consolidated criteria for reporting qualitative research (COREQ) guideline.¹⁹

Participants

This qualitative study was conducted at the Cancer Hospital of Henan Province, China, a tertiary care facility, in March 2021. Inclusion criteria were: 1) had been prescribed OTAD for at least 14 days for lung cancer treatment (most patients were allowed to take the drugs home for 14 days); 2) age greater than 18 years; 3) over 6 months of survival; 4) able to consent for themselves; and 5) perform effective oral communication. The samples were selected based on a maximum variant strategy in terms of levels of education, family structure, different ages and disease stages. This sampling strategy enabled the researchers to capture a wide range of views and experiences from patients. In the current

study, totally 59 lung cancer patients were recruited, 40 of whom passed the screening criteria. Eventually, 30 patients consented to the qualitative interview. Patients refused to participate mainly because of a lack of interest, fatigue, or inconvenience. Probing questions were incorporated in this work in order to gain further information from the interview. Data redundancy and information saturation were observed after 21 interviews, thus the interviews were ceased.

Data Collection

The interview checklist included demographic information, disease information and a probing question of attitudes or experience in adherence to medication therapy. The list of interview content was compiled based on previous relevant studies and reviewed by one clinical nursing specialist and three oncologists. To ensure the rigor of the interview questions, we conducted four pretest interviews and refined the list based on the interview results. The final list of interviews is shown in Table 1. Semi-structured interviews are generally held at a place preferred by the participants, and the place should be quiet and hidden. In order to encourage participants to talk about their experiences or thoughts, the interview began with an open question: “What medication are you taking?”

An audio recorder was used to record the responses of patients to all questions. The interview was conducted by a researcher and a nurse. The researcher mainly discussed relevant issues with the interviewees, the nurse focused on recording their movements, facial motions and body language (eg laugh, cry, frown ...) to better reflect the emotions and thoughts of the participants. Each interview lasted approximately 50 to 70 minutes. Demographic data were obtained from their medical records at the end of the interview to avoid interrupting the narrative flow of the interview.

Data Analysis

After the interview, the record was transcribed into text by We-Chat software within 24 hours, and each transcribed text was anonymously coded as P1, P2 The transcript was read by two independent researchers line-by-line to check for accuracy. When there were new explanations emerged, researchers would provide feedback to each other. At the same time, the conflicting statements of patients such as the use of different names of the same medicine were double-checked. Finally, the written materials were sent to the interviewees via email for verification. In this study, the interviewees had no objection to the completeness and accuracy of the written materials.

Data were analyzed using thematic analysis. The following analysis procedures had been carried out: 1) two researchers (A and B) independently read the transcript; 2) A and B independently extracted data from the first five interview transcripts to formulate initial themes and sub-themes; 3) A and B discussed findings and agreed on a preliminary set of themes and sub-themes. After each interview, they analyzed the data to find new findings. Themes and sub-themes were determined following analysis of 19 interviews; 4) A third researcher (C) repeated the

Table 1 Questions Guiding the Interview

1. What medication are you taking?
2. What does it mean for you to adhere to the medication?
3. Have you taken the medicine as prescribed by your doctor? If yes: What makes you insist on taking medication as prescribed by your doctor? If no: What has prevented it? What are the manifestations of non-compliance with the doctor's medication?
4. What is your experience about adherence to OTAD?
5. Did oral targeted drugs bring you side effects? How do you deal with side effects?
6. What can you suggest to improve adherence to drug administration?

Abbreviation: OTAD, oral targeted antineoplastic drug.

process with the remaining two texts, verifying themes and sub-themes; 5) After discussion, three researchers agreed on the final set of themes and sub-themes that adequately represented the data set. Themes generated were mapped against WHO determinants of medication adherence that included patient-related-, health system/ healthcare team-related-, therapy-related-, condition-related-, and social/ economic-related factors.²⁰

Ethics

This research was approved by the Ethics Committee of Zhengzhou University (Approval No.2021-22). The whole research was also in line with the Declaration of Helsinki. The clinicians explained clearly about the potential benefits of this study to the participants. And at the same time, the clinician emphasized that no any form of discrimination would occur even if patients refused to join. All participants were given written and verbal information about the study and received their acknowledgment. All the patient-related identifiable information has been removed from the transcripts.

Results

Totaling 17 male and 4 female patients were interviewed. Fifteen participants were >50 years old. Almost all participants previously received surgery and chemotherapy. Data from 21 participants were analyzed, with 15 patients being not fully adhering to the medication regimen. After analysis, the demographic characteristics of patients were presented in Table 2. As shown in Table 3, this analysis led to the extraction of four main categories, each with several subcategories.

Patient-related factors

Medication-Taking Introspection

The introspection on medication was mainly the judgment of drug efficacy made by the respondents after accepting the medication regimen. It was found that there was a clear correlation between good treatment experience and high medication compliance. As shown in this study, patients who tended to stick with the treatments were normally those who had shown a more positive treatment effect during early treatment (P2; P8). In particular, patients who had experienced severe side effects after chemotherapy and/or radiotherapy were more likely to choose targeted drugs (with milder side effects) (P13; P15; P21).

Family Structure

The family structure of patients is one of the key factors affecting patients' attitude towards treatment. A young family with underaged children would encourage patients to maintain a high degree of adherence (P1; P4; P11; P17). Conversely, due to concerns about financial and spiritual pressure of their family members, patients with mature family structure (most of the family members are adults) tended to show a negative attitude towards treatment (P5; P7).

Weigh the Pros and Cons of OTAD Treatment

During receiving OTAD treatment, what is a major issue for patients is to weigh two pairs of factors, ie, drug side effects vs disease severity and economic burden vs life expectancy. Patients who had suffered from the treatment-related side effects for a long period generally showed negative attitudes towards treatments (P8; P12; P14; P21). Regarding the economic burden and survival period, patients replied that if they could survive longer, they would more likely to take medication even bear heavy treatment expenses (P15; P16). When we talked about whether they would consider giving up treatment, most people said that if they were informed that they could live for less than half a year, they would give up all treatments, including taking medicine, to reduce unnecessary expenses (P3; P11; P17). But, some patients indicated that they would continue their treatments until they were informed that there were only three months left (P1; P9, P19).

Table 2 Demographic Characteristics of Participants

Characteristics	N=21
Sex	
Male	17
Female	4
Age (years)	
30–40	1
40–50	5
50–60	9
>60	6
Stage at diagnosis	
Stage II b	2
Stage III	15
Stage IV	4
Level of education	
Primary school or less	5
Secondary school	13
College degree or above	3
Oral antineoplastic agent	
Gefitinib	7
Osimertinib	4
Afatinib	6
Icotinib	4
Marital status	
Married	19
Divorced	2
Unmarried	0
Previous treatment	
Surgery	18
Chemotherapy	20
Radiotherapy	8
Targeted therapy	5

Medication-Related Factors

Medication Experience

It was more likely for patients to follow doctor's instructions if they had previously undergone other anticancer treatments (other than OTAD), especially, when patients had suffered from the side effects of the previously used medication. It was also found that patients were more likely to follow doctors' instructions if the treatment effects of the previous medications had been compromised due to their non-adherence with doctors' instructions (P5; P16; P21).

Adverse Reactions

During OTAD treatment, the potential adverse reactions is a major concern of patients. Due to patients having different tolerances to the side effects of OTAD, they differ in the compliance behaviors. Some patients might continue to take the medicine even if the negative effects were obvious while others might easily give up treatments even facing mild side effects. However, it should be mentioned that in many cases, these affected patients normally give up certain types of drugs (or seek alternative drugs for milder adverse reactions) rather than completely give up the treatment (P7; P8; P14; P19; P20; P21).

Table 3 Summary of Themes and Sub-Themes Derived from Analyses of Text and Focus Records

Themes:	Sub-Themes and Quotes:
I Patient-related	<p>Medication-taking introspection “It’s (OTAD) less painful than chemotherapy, and it doesn’t require infusion for a long time. My disease is under good control.”</p> <p>Family structure “I have to take medicine actively so that I could get another time to look after my two babies.” “The high cost of treatment is such a great burden and makes us poor.”</p> <p>Weigh the pros and cons of OTAD treatment “I often think about whether taking gefitinib in continue has any point.” “Taking medicine every day makes me feel very irritable (cry).”</p>
II Medication-related	<p>Medication experience “Comparing with previous regimen, the effect of the osimertinib prescribed by the doctor is very good, which makes me feel better.” “I have been taking it for a long time, and everything going well.”</p> <p>Adverse reactions “Taking icotinib broke me out in a rash, I could not sleep every day (frown). “Doctor’s suggestions were ineffective, so I gave up it (icotinib).” “It (afatinib) makes me feel pain in my limbs just like needles in my legs and feet, but I still insist on taking. I can live with that (pain).”</p> <p>Information access “The information (OTAD) I received from my relatives was not consistent with what my doctor told me. I had more trust in my relatives, so I rejected my medication regimen.” “When someone said that a doctor could helped my relief symptoms, I would couldn’t resist seeking help”.</p>
III Doctor/nurse-related	<p>Shared decision making “I want to know why I have to take these drugs. If I don’t understand, I really feel uneasy.” “I only took it (icotinib) for two months because I couldn’t afford it, but they (doctors) strongly recommended to me.”</p> <p>Doctor’s reaction “I was disappointed that the doctor ignored my pain. That makes me sad. I am not willing to take it (afatinib).” “I think they only care about what they want to hear while don’t have any patience to answer my questions.”</p> <p>Nurse’s inquiry “The nurse always reminds me to take medicine which just likes a alarm clock to prevent me from forgetting to take icotinib.” “They (nurses) were happy to tell me something about the medication administration if I asked.”</p>
IV Society related	<p>Stigma “I refused to take afatinib in the presence of other people. I am worried that they would be afraid to be with me after knowing my situation.” “I don’t want to be labeled as a cancer patient.”</p>

Abbreviation: OTAD, oral targeted antineoplastic drug.

Information Access

Patients’ knowledge about disease and drug information comes from two aspects, one is through actively seeking knowledge, and the other is through passive exposure to public/social media (advertising, news, etc.). The more knowledge patients had, the stronger self-determination they would be. For example, if they had a deep understanding of the pathology of their diseases and the mechanisms of action of the OTAD medicines, they would be inclined to make independent decisions about whether take medicine as prescribed or not (P10; P16; P20). On the contrary, patients who lack disease-related knowledge might be more compliant and cooperative to doctors’ suggestions (P18). As for public media, it has been suggested that network information and TV advertisement could also affect patients’ medication behaviors. In some cases, patients could be misled into giving up prescribed medications by other medicine (herbal medicine) advertisements that exaggerate the efficacy of the treatment (P11; P12).

Doctor/Nurse-Related Factors

Shared Decision Making

Due to the lack of knowledge about novel targeted drugs and the complexity of combination therapeutic regimens, patients may not understand the causes and information of the drugs they are taking. Therefore, patients strongly desire to get drug information and participate in shared decision-making (SDM) so that they could gain opportunity to choose drugs regimens. If doctors do not allow patients to join in SDM, patients who know little about treatment regimens may be resulted in poor treatment adherence because of distrust (P3; P7; P8; P11; P16).

Doctor's Reaction

This subtopic suggested that the physicians' responses to drug side effects could affect patients' judgment and medication preference to OTAD. Both indifferent and negligent attitudes of physicians could cause patients' doubts and distrust. In cases when physicians had no effective measures to alleviate adverse reactions, patients might refuse to accept further treatments or even give up treatments (P1; P5; P6).

Nurse's Inquiry

As the executors of treatment and responsible for providing knowledge about the applied treatments, nurses are a key channel for patients to obtain medication information. The high-frequency and effective health inquiries from nurses could help patients develop a sense of trust and improve their awareness of taking medicine. Also, nurses could provide physicians with feedback about the treatment, which could in turn remind doctors to pay close attention to patients' treatments (P1; P6; P7).

Society Related Factors

The main social barrier for effective OTAD treatment is the stigma associated with cancer. Because of the existing cognitive biases such as cancer is infectious or cancer brings bad luck, people might stay away from cancer patients. As a result, patients might feel ashamed and show some improper behaviors such as withholding their medical history from doctors, avoiding taking OTADs in the presence of others, or even being reluctant to talk anything about their medicine schedules (P12; P18; P20; P21).

Discussion

As shown in this work, factors that affect lung cancer patients' persistence in taking OTADs fall under four categories: patient, medication, doctor/nurse, and society. Specifically, factors such as medication experience (efficacy and toxicity of medicines), medication-taking introspection, doctor's reaction, cancer stigma are consistent with previous findings.^{13,21–26} These factors are the key points for evaluating the medication adherence of patients.

When family structures were considered, it was clear that in the younger families (patients' children are the younger), patients tend to be more positive, which could make them have better compliance with OTAD treatment. This is understandable for reason that parents always want to get the opportunities to see their children to grow. The pursuit of family time was a key motivation for patients with young families.²⁷ On the other hand, patients with a mature family structure are prone to give up their treatments, therefore more family support may be required for this group of patients.

Interviewees tended to weigh the gains and losses related to OTAD treatment (eg, prolonged life expectancy vs economic burden and side effects) when reflecting on their treatment experiences. The side effects of targeted drugs vary from person to person.²⁸ Advanced cancer patients were distressed by the unalterable outcome of their illness (death) or frustrated by their inability to resolve problems with diet and daily living. They were more likely to stop OTAD therapy without notifying their doctors. Besides, targeted drugs are normally costly. Even with subsidies from Medicare or private insurance, the remaining part of payouts may prevent patients from receiving treatment.²⁹ Such a situation was often due to doctors failed to have a specific discussion about the costs with patients in the early stage of treatment, or patients underestimating the economic pressure brought by continuous treatment.³⁰ Therefore, in order to enhance adherence to OTAD treatment, healthcare providers should take measures to minimize underlying conditions (dermatitis,

diarrhoea, etc.) which might cause side effects and have a discussion with families regarding the cost of treatment before prescribing OTAD.

For the theme “information access”, what can not be ignored is that the false/ incorrect medication information received by interviewees might develop into a significant obstacle of medication compliance. Misleading information such as exaggerated disease severity and side effects of drugs could increase negative attitudes of patients. This could eventually caused patients stop treatment when even normal physical discomfort appear. In fact, not all side effects are bad signals as some toxic manifestations may implicate the treatment is in effect (eg, skin toxicity of EGFR inhibitors).²¹ It may be necessary for healthcare providers to encourage patients to adhere to medication by checking the authenticity of the information they received from relatives, advertisements or the Internet, and actively provide patients with up-to-date drug information.

Patient-centered philosophy makes SDM increasingly important, as it can not only encourage patients to accept treatment options as suggested by doctors, but also help to improve medication adherence.³¹ As shown by Kirk’s study, a good comprehension of the clinical importance of agents could help more than 90% of patients to adhere to therapy.³² Unfortunately, in many cases, clinicians did not invite patients to join in the discussion of OTAD options. In the opinion of most doctors, it is futile to involve patients in SDM to improve their compliance. The reasons might be due to insufficient training of physicians or due to doctors’ thoughts that patients might have limited knowledge in medicine.³³ Actually, respondents indicated that they expected to join the SDM and learn about the efficacy and the importance of proper treatment schedules. In the future, health care providers should consider patients’ choices for the treatment and let them learn about the treatment effects and side effects of OTAD. This may make patients become more cooperative with the doses, treatment schemes, potential outcomes of the therapy.

It was reported by patients that the individual who had poor interactions with nurses displayed poor compliance. Nurses’ inquiry about medicine was a positive factor for promoting patients’ medication adherence. Patients said that it was the nurse who reminded them to take their medicines on time, and the information they had learned from nurses even exceeded that from doctors. Therefore, we suggest that nurses should maintain regular conversations with patients to encourage patients to put forward ideas and suggestions for their treatments, and actively provide feedback on patients’ demands. Furthermore, it is important for nurses to promote nurse-patient-physician collaboration for improved medication adherence. This is because a good sense of trust could make patients follow the medication suggestions of healthcare providers for a long time.

Limitation

Although we endeavor to faithfully reflect the opinions and suggestions received from the interviewed patients, we acknowledge that our interpretation was inevitably subjective. In this study, due to a quantitative method was not applied, the replies from patients could be somehow subjective and potentially lead to biased results. In addition, given the different health care standards in different regions of the world, the influence factors identified in this study (performed in central China) may not suitable to be generalized to patients in other places. Thus, more qualitative studies should be conducted in different contexts or in different populations.

Conclusion

To our knowledge, this is the first qualitative study to explore the adherence of oral targeted drugs in lung cancer patients. This study indicated that OTAD-taking behavior of lung cancer patients is associated with multiple factors including family structure, weighing the pros and cons of OTAD treatment, information access, shared decision making, nurse’s inquiry. For improved medication adherence, it is necessary to invite patients to join in SDM, and from the side of healthcare providers, to actively promote patient-nurse-physician collaboration. Furthermore, considering the influence of family structures on drug adherence, developing patient-centered intervention programs via providing up-to-date medical information and psychological support to patients may be necessary. Future research should emphasize on how to apply these identified factors to help healthcare providers to promote the medication adherence of lung cancer patients to OTAD treatments.

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Disclosure

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