Adverse Reactions of Targeted Therapy in Cancer Patients: A Retrospective Study of Hospital Medical Data in China

Ruofei Du  
The college of nursing and health of Zhengzhou university

Lixia Ma  
School of statistics, Henan university of economics and law

Leon M. Larcher  
Center for comparative Genomics Murdoch university

Han Tang  
The college of nursing and health of Zhengzhou university

Huiyue Zhou  
The college of nursing and health of Zhengzhou university

Changying Chen  
The First Affiliated Hospital of Zhengzhou University

Tao Wang  
Research article

**Keywords:** Adverse Reactions, Cancer Patients, Hospitalization, Targeted Therapy

**DOI:** https://doi.org/10.21203/rs.3.rs-70708/v1

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Abstract

Background: The adverse reactions (ADR) of targeted therapy were closely related to the treatment efficacy, quality of life (QoL) and prognosis of cancer patients. However, few studies analyzed the ADR of targeted therapy and their effects on cancer patients. This study was conducted to describe the incidence and characteristics of ADR in cancer patients with targeted therapy and outcomes associated with ADR based on hospital medical data.

Methods: A retrospective secondary data analysis was conducted using ADR data in hospital medical record collected from a cohort (n=2,703 with targeted therapy) in three hospitals of Henan, China from January 2018 to December 2019. The type, classification, occurrence time and duration of ADR, medication compliance and drug application, QoL, disease progress and survival of patients were analyzed.

Results: A total of 485 patients met the inclusion criteria. 296 (61.0%) patients had ADR during target therapy. The top five ADR in this study were damage to skin, fatigue, mucosal damage, hypertension and gastrointestinal discomfort. 62.1% of the ADR were mild to moderate, more than half of the ADR occurred within one month, 68.6% ADR lasted more than one month. Older patients ($P=0.022$) and patients with lower education level ($P=0.036$), more than 2 comorbidities ($P=0.021$), longer medication time ($P=0.022$), drug combination ($P=0.033$) and intravenous administration ($P=0.019$) were more likely to have ADR. Those who had ADR were more likely to stop taking ($P=0.025$), change ($P=0.010$), adjust ($P=0.019$), or not take the medicine on time ($P=0.022$), or undergo cancer recurrence ($P=0.027$) and show higher rates of metastasis ($P=0.009$).

Conclusion: The incidence of ADR in cancer patients during targeted therapy was high. Age, education level, comorbidity and medication strategy can affect ADR. Furthermore, ADR would affect the treatment and prognosis of patients. We should pay more attention to these ADRs and develop effective management strategies.

Background

According to the latest global cancer data report, there are approximately 18.1 million new cancer cases in the world in 2018. In China, the incidence and mortality were far higher than the global average level. In 2015, 3.299 million people in China had been diagnosed with cancer, with an average of more than 10 thousand people per day. 7.5 people per minute were diagnosed with cancer, thus cancer has emerged as a major health problem worldwide(1). A study showed the 5-year survival rate of patients with advanced metastasis is only 2% ~27% following traditional treatment methods such as chemotherapy and radiotherapy(2). It is difficult to further improve the treatment efficacy of traditional treatment due to the limitations caused by toxicity and ADR(3). The development of precision medicine, which fully considers the individual variability and differences between patients' treatment strategies. With the development of gene technology, we can classify different cancers based on their specific molecular signals. These
advances have further allowed the identification of molecular therapeutic targets specific to cancer cells, thus providing a framework whereby therapies can be specifically matched to corresponding molecular targets(4). By targeting the complex network of signaling pathways that regulates cell proliferation, angiogenesis, and apoptosis (cell death), researchers have developed new targeted agents that interfere with the growth and proliferation of cancer cells(5).

Several studies had shown that targeted therapy could improve the overall survival (OS), progression-free survival (PFS), and response rate (RR) of cancer patients(6). Moreover, compared with chemotherapy, targeted therapy has lower toxicity, better tolerance and reduced hospitalization time(7). However, although the lethal ADR is lower than chemotherapy, targeted drugs need to be daily for extended periods or even indefinitely, therefore, the incidence of ADR of targeted therapy can be as high as 80% due to the long-term administration and the characteristics of targeted drugs(8). The main characteristics of the ADR caused by targeted therapies are as follows: they are common and involve multiple organ systems of the human body; the ADR of different targeted drugs are different (in terms of types, frequency and severity); most of the ADR occur in the early stage and will not aggravate with the progress of treatment; most of the ADR are mild, which can be effectively controlled by standard care; a small part of the ADR are intolerable to patients which require for discontinuation or other interventions. Therefore, it is very important to control the ADR to achieve optimal clinical medication and patient outcomes(9).

According to a recent study, the incidence of ADR during the targeted therapy could reach as high as 86.4%(10), and occurred commonly in skin and mucous. In addition, gastrointestinal reactions, hypertension, coagulation disorders and cardiotoxicity were also common ADRs, which led to poor compliance, resulting in the negative impact on the QoL and daily activity of cancer patients(11). Some researches indicated that about 32% of the patients receiving targeted molecular treatment experience unplanned discontinuation due to adverse reactions, which lead to poor therapeutic effect, prognosis and even lead to cancer recurrence or progression(12).

Overall, it is imperative to focus on the ADR of targeted therapies to improve the treatment efficacy and the QoL. To this end, we should not only deal with the common ADRs but be alert to the difficult ones(13). At present, there are few studies focus on the ADR of targeted cancer therapy. Even so, most studies only described the types and degree of ADR, and did not investigate other characteristics such as time and duration of ADRs of the treated cancer therapy-related ADR(14). Moreover, few studies explored the impact of ADR on the outcome and prognosis of patients, and had little exploration on the situation of targeted drug treatment(15). To provide insights in this area, the current study, the current study was designed to describe the incidence and characteristics of ADR in cancer patients who underwent treatment with targeted therapies and to investigate outcomes associated with ADR based on hospital medical data retrospectively. We aim to understand the actual situation and ADR of targeted therapies in cancer patients. We also aim to understand the impact of ADR on patients, then to provide basis for clinical workers to effectively identify and accurately evaluate ADR and carry out targeted intervention measures.
This study was guided by the theory of symptom experience model (SEM)(16). The SEM provide a complete definition of symptom experience, including antecedents, symptom experience, process and result. The main content of the model is symptom, and the symptom experience has four aspects, including the perception of symptom frequency, intensity, perplexity and symptom meaning; the influencing factors (antecedents) contain demographic characteristics, disease characteristics and individual characteristics. Outcome indicators are the results of symptom experience, including adjustment to illness, QoL, mode, functional status, disease progression and survival. This study focuses on influencing factors from 3 aspects in this theory and symptom experience caused by targeted therapy. Meanwhile, we choose outcome indicators according to the consequences of SEM. Framework of this research is shown in Fig. 1)

Methods

Aim

To describe the incidence and characteristics of ADR in cancer patients with targeted therapy and outcomes associated with ADR based on hospital medical data.

Study design, setting and sample

A retrospective cohort design was employed with analysis of routinely collected prospective data from medical records which was conducted by three nurses that deliver healthcare services in the oncology department of three hospitals in Henan, China. Electronic medical records (EMRs) of cancer patients who received targeted therapies from Jan 2018 to Dec 2019 were reviewed. Patients’ records were included in the analysis if they (1) were cancer patients with targeted therapy and (2) were more than 18 years old. As we used de-identified, administrative data, informed consent was not required. The sample frame was refined to include 1897 clients.

Population selection and data variables

Medical and nursing records that were incomplete or cannot be analyzed and records with incomplete ADR names were excluded. Moreover, according to the ADR / Event Association Evaluation Criteria in the guidelines for the use of ADR terms, the reports with "possibly unrelated" and "unable to be evaluated" were excluded. Finally, 485 patients were analyzed. There were 296 patients with an included code for ADR. The variables were selected according to the framework of the research (Fig.1). We examined the following areas: patients’ socio-demographic characteristics (age, gender, education level, socioeconomic status, etc.); disease characteristics (disease stage and type, drug use, comorbidities: calculated as the number of chronic diseases included in the Charlson Comorbidity Index (CCI)), ADR (type, intensity, start time, duration); treatment compliance (discontinuing medication, change medication, dose adjustment, take medicine on time); disease progression (recurrence, metastasis); survival.

Data collection procedure
The de-identified EMRs data was collected by nursing staff working in the oncology department in three hospitals and three graduate nursing students in Zhengzhou university. The student who was extensively involved in the ADR study trained the other two students to extract data. Interrater reliability was 98%~100% between the trainer and the other two students. The data was obtained from medical and nursing records and consent documents. The data was coded anonymously according to Preferred terms (PT) of Medical Dictionary for Regulatory Activities (MedDRA)(17). The patients were divided into ADR group and none-ADR group according to whether they had an ADR or not.

**Statistical analysis**

Data were entered into the SPSS version 21 (IBM, Armonk, NY, USA) for descriptive analysis. Continuous data were presented as mean and standard deviations or as medians and interquartile ranges, categorical variables were presented as proportions with 95% confidence intervals. In a matched study design, unlike in case-control studies, there is no need to account for the matching in the analysis and, therefore, the descriptive statistics for the two broad groups were displayed.

Univariate and multivariate logistic regression with backward stepwise selection were used to examine any differences in the characteristics of cancer patients with undergoing targeted therapy using a dichotomous outcome representing patients with ADR or not. Logistic regression models were developed with the dependent variable of ADR. The independent variables of interest were the other variables available in the EMRs.

**Results**

**Socio-demographics**

A total of 1897 patients were screened for enrollment, and 1412 patients were excluded based on the selection criteria. Finally, 485 patients were analyzed in the study (Fig. 2). The socio-demographic characteristics of the included cancer patients are outlined in Table 1. About 61.0% of the patients had ADR.

**Factors Associated with ADR**

The univariate comparison showed that age ($P=0.019$), education level ($P=0.017$), CCI ($P=0.003$) and cancer type of lung, gastric and colorectal cancers ($P=0.008, 0.007$ and $0.006$ respectively), duration of treatment ($P=0.004$), combined treatment ($P=0.028$) and intravenous administration ($P=0.034$) were significantly different between these two groups, while age, education level, comorbidities, duration of medicine, combination of medicine and route of administration were independent factors for ADR by multivariate logistic regression. (Table 1 and Table 2).

**Characteristics of ADR**
Of the patients who had ADRs, some patients had more than one kind of ADR. There were a total of 646 ADRs as detailed in Table 3.

**Treatment compliance, disease progress and survival according to ADR**

Compared with patients in the non-ADR group, those in ADR group were more likely to have worse treatment compliance (Table 4). Discontinuing medication, changing medication, adjust drug dosage, not taking the medication on time were more common in the presence of ADR. 62.2% (84/296) of patients in ADR group stopped taking the medication when they suffered from ADR, 33% (98/296), 53% (157/296) and 62.8% (186/296) of patients changed, adjusted and did not taking the medication on time, respectively. Patients with ADR were more likely to have cancer recurrence and metastasis. There were no statistical differences for death between these two groups (Table 4).

**Discussion**

According to this study, people with ADR had different socio-demographic characteristics, treatment compliance, disease progression and survival compared to those without ADR. Our work expands on previous studies by providing a comprehensive examination of a large population of outcomes related to ADR in patients who underwent targeted therapies. To our knowledge, few studies had examined the features of ADR of targeted cancer therapies. Previous studies only investigated the type and intensity of ADR, but did not discuss the occurrence time and duration of ADR. In addition, no study reported outcomes related to ADR and impacts on patients in China. Through this research, we found some of patients’ characteristics such as age, education level and comorbidities and some treatment strategies, such as combinatorial treatment and administration route were associated with ADR. Meanwhile, we summarized more comprehensive characteristics of ADR, including the types, grading, occurrence time and duration, which made up for the incomplete evaluation and analysis of ADR. Patients with ADR had poor treatment compliance, and experienced a higher rate of discontinuation, change and adjustment of medication, and tended to not taking medicine on time. Moreover, patients with ADR had higher rates of cancer recurrence and metastasis.

In this study, 61% patients who underwent a targeted therapy had ADR, which was lower than previous observations (18, 19). In fact, the proportion of patients with ADR in this study was far more than 61%. This is because that the medical records only showed that the patients had ADR, but the type of ADR was not recorded or the information was incomplete, which led to these patients being excluded from the final analysis. This study showed age and comorbidities were influencing factors of ADR, and older patients and patients with more comorbidities were more likely to have ADR which was consistent with the study conducted by Tristan and Daud et al (20, 21). It may be related to the decrease of drug metabolism and the damage of liver and kidney function in the elderly. Additionally, comorbidities made patients suffer from complicated conditions, comorbidities may also result in the use of a number of medications which could contribute to the ADR caused by drug interaction. Furthermore, the interaction between diseases may lead to worse physical, emotional and social function (22). The study highlighted the importance of
health education. We concluded that the education level of patients affected the occurrence of ADR. When the underlying reasons were investigated, it was found that patients with low education level lacked understanding of targeted therapies, and therefore had difficulty accepting and understanding health information related to drug use. Such patients had limited access to knowledge, weak perception of disease and lack of awareness of active learning. Research showed that more than 90% of patients undergoing targeted therapy thought that it was necessary to know drug-related knowledge and to solve ADR through health education by medical staff(13).

Therefore, medical staff should pay more attention to elderly patients and patients with more comorbidities. We should know and monitor the disease changes, treatment strategies, drug efficacy and medication of elderly and comorbid patients. What’s more, it is very important to strengthen early assessment and risk management, which are of great significance to improve drug response and reduce ADR. At the same time, we also suggest guiding the elderly and comorbid patients to carry out self-management, and to remind and supervise patients to implement ADR management. By giving effective health education, we can improve the understanding of targeted therapies and the ADR of these patients, allowing them the ability to become familiar with the drugs they used(23). We should also teach patients to record utilize medication diaries and assist patients into managing comorbidities, in order to balance the application between other drugs and targeted drugs. Moreover, we should try to prevent the ADR of targeted therapies in advance, visit patients before targeted treatment to evaluate and review patients, then discuss with patients to develop educational goals and plans to facilitate ADR prevention.

Combined treatment and route of drug administration may affect the ADR of targeted therapies, which has been confirmed by Staats, Jui-Chun, and Bhullar et al.(5, 24, 25), and is consistent with our research. This study indicated that the duration of drug administration didn’t affect the ADR of targeted therapy, which was consistent with Muro(26). The ADR of drugs were mostly caused by the components of the drugs themselves. Although the toxicity of these drugs didn’t change over time, some toxicity appeared earlier while some later. After intravenous administration, drugs rapidly distributed to the whole body. Drugs without metabolism and detoxification can not only kill tumor cells but also damage normal tissues and organs, thus causing ADR in multiple systems / organs(27). When various drugs were used together, the physicochemical properties, drug reactions, metabolism and excretion may interfere with each other. At the same time, the accumulation of toxic components in the body increased the possibility of ADR(28). Therefore, it is necessary to formulate reasonable drug treatment strategies, enhance the awareness of rational drug use, and closely monitor the drug administration and use.

We can see that the top five ADR in this study were damage to the skin, fatigue, mucosal damage, hypertension and gastrointestinal discomfort. Most of the ADR of targeted therapy were chronic(15), we found more than half of the ADR occurred within one month. However, there were also some ADRs such as cardiotoxicity, which occurred immediately after administration. A few ADR such as thrombosis and interstitial pneumonia may appear after three months of administration. For the most common ADR of skin, 60% of the patients had skin ADR within one month after treatment. Among them, acneform eruptions appeared in the first two weeks of treatment, 46.5% of patients had dry skin in the first month,
and paronychia was more common after two months of treatment. During this study, ADR was graded according to the latest CTCAE 5.0 standard issued by the U.S. department of health and human services in 2017(14). We concluded that 84.2% of ADRs were mild to moderate in severity, which was consistent with the view that the degree of ADR of targeted therapies was lower than that of chemotherapy(7). The more severe ADR included cardiotoxicity, coagulation dysfunction and interstitial pneumonia, these ADR were mostly fatal. Generally, skin ADRs were mild, but severe rash can also lead to death. Another characteristic of the ADR of targeted therapies was that the duration of ADR was long. 68.6% ADR of the patients in the study lasted for more than one month. In addition, most of the ADR occurred repeatedly, and pulmonary fibrosis caused by interstitial pneumonia was even permanent.

As for the impact of ADR on patients and ADR related outcomes, we collected data on treatment, disease progression and prognosis, including drug use, recurrence, metastasis and death. We observed that due to various ADR, patients may change treatment programs and drugs, adjust drug dosage and even discontinue treatment. Meanwhile, patients with orally administered drugs stopped taking medication and reduced drug dosage, due to being unable to tolerate the ADRs. Therefore, the compliance of patients with orally targeted drugs decreased, while the incidence of missed dosages and not taking drugs on time increased, this was confirmed by Sano et al(12). In this study, 62.2% of patients stopped taking drugs and 62.8% did not take drugs on time due to adverse drug reactions. ADR resulted in negative impact on the QoL, physical function, daily activity, social and emotional function of cancer patients, which reduced the desire of patients for treatment, affected their work and study, so as to make patients resist taking medicine(11). What’s worse, these patients suffered for a long time, resulting in the sense of helplessness and apparent social participation disorder, anxiety and psychological distress, these were all reasons why it was difficult for patients to carry out treatment smoothly. In this study, more than 30% of patients had cancer recurrence or metastasis. Because of the poor compliance, the drugs did not achieve the desired effect so that the ability of drugs to control and treat the disease was declined too, which led to the recurrence and metastasis of cancer(29).

Advantages and limitations

Our study supplemented the situation in mainland China about ADR of patients who received targeted therapies. Previous studies only analyzed the type and classification of ADR, but we comprehensively interpreted the characteristics of ADR, further discussed the start time and duration of ADR, and explored some influencing factors of ADR. Moreover, our research was based on SEM theory, which provided the basis for determining the research program and the selection of variables in the research. However, it is necessary to highlight some limitations. A lot of ADR information in the EMRs reviewed in this study were missing or incomplete, which indicated that sometimes, there was no reporting or recording of ADR in clinical practice, or there was no standard ADR records, which leaded to difficulties in extracting information and means that the results could be biased. The reasons may be that most of the ADR were chronic and not serious, so, medical staffs were not aware of the importance. It should be noted that we had reviewed only the last two years so that data collection is limited. However, there was no difference in the outcome of death between ADR group and non-ADR group, it may require a longer duration to review.
Similarly, although we found differences in recurrence and metastasis outcomes between the two groups, a longer-term review may be more meaningful. At the same time, the impact of ADR on patients and the prognosis of the disease also includes the quality of life, functional status, psychological status, OS and PFS of patients, the analysis of these indicators is of great significance to clinical practice and theory, but the retrospective study can not achieve, so, it needs further prospective research. Therefore, the results might be unsuitable to be extended directly.

**Implication**

This study provided data on ADR of cancer patients with targeted treatment, and analyzed the influencing factors and outcomes of ADR, which indicated important information for medical staff, allowing them to pay more attention to ADR of targeted treatment of cancer patients. Meanwhile, the results of this study promoted the identification, monitoring, evaluation and recording of ADR and provided ideas and premise for intervention research of ADR. Furthermore, we supply a reference for clinical practice, in order to help and improve clinical decision-making. Additionally, the results of this study were of great significance to promote the safety of patients, and provided the basis for further understanding the ADR of targeted therapies and the factors that should be paid attention to during medication administration and use. On the other side, health-care providers should pay attention to the factors identified in this study and consider the following strategies: (1) Attention should be paid to the contraindications of drug use in special population in order to avoid unreasonable/dangerous combinations of drugs; (2) The usage, dosage, course of treatment should be strictly monitored; (3) Evaluating and recording ADR in time, and developing standardized ADR terms according to the specific national conditions/priorities in China in combination with the existing international standardized terminology; (4) Strengthening Health education; (5) Promote the development of ADR management indicators which contributes to measurement of the quality of ADR management and patient satisfaction, and achieving patient-centered interdisciplinary cooperation.

**Conclusion**

The incidence of ADR in cancer patients during targeted therapy was high, with different features involving various systems/ organs. Most of ADR were mild to moderate in severity, while some were lethal. These ADRs were mostly chronic and occurred after one month of administration. Some ADR existed during the treatment or even had permanent damage. Age, education level, comorbidity and medication strategy can affect ADR, while ADR can affect the treatment and prognosis of patients. Therefore, the characteristics, influencing factors and outcomes of ADR obtained in this study can accumulate experience for clinical staff to carry out ADR management, to improve the treatment effectiveness and ensure the safety of patients.

**Abbreviations**
Declarations

Ethics approval and consent to participate

The current study was part of an internal hospital project related to the improvement of the quality of life in cancer patients; thus, it was exempt from the need for approval by Institutional Review Board of Zhengzhou University. We used the data in EMRs so we do not need participants’ informed consent also.

Consent for publication

Not applicable.

Availability of data and materials

The data generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author who was an organizer of the study.

Conflict of interest

No conflict of interest has been declared by the authors.

Funding statement

1. The National Natural Science Foundation of China (No.81773175)
2. China Postdoctoral Science Foundation in 2018: (2018M630839)

Authors’ contributions

WT and CCY were responsible for the overall design and quality control of the study as well as the communication with the hospital and departments reviewed. DRF contributed to the implementation of the research and the training and management of nurses and students who collected data. DRF, WT and LML contributed to the conception of the study, drafting and critical revision of the manuscript, and provided final approval of the manuscript, MLX contributed to data analysis and solving statistic problems.

Acknowledgement

We thank the First Affiliated Hospital of Zhengzhou University, Cancer hospital and the First Affiliated Hospital of Henan University of science and technology for their assistance and support, and the data provided by the information Center of these three hospitals. We thank the graduates from the college of
nursing and health of Zhengzhou university. We thank School of Statistics, Henan University of Economics and Law and Murdoch University for their supports. We also thank the nurses of the two hospitals.

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Tables

Table 1 Demographic and disease-related characteristics among patients with or without a ADR (univariate logistic regression)
| Characteristics                      | Cases, n (%) | ADR With, (%) | Without, n (%) | OR a (95% CI) | P value |
|-------------------------------------|--------------|---------------|----------------|--------------|---------|
| All                                 | 485 (100)    | 296 (61.0)    | 189 (39.0)     |              |         |
| Mean (SD)                           | 63.4 (11.8)  | 67.8 (12.6)   | 59.5 (11.3)    |              |         |
| Age                                 |              |               |                |              |         |
| ≥60                                 | 294 (60.6)   | 202 (68.2)    | 92 (48.7)      | 3.247[1.564-7.681] | 0.014* |
| <60                                 | 191 (39.4)   | 94 (31.8)     | 97 (51.3)      | 1            |         |
| Gender                              |              |               |                |              |         |
| Male                                | 261 (53.8)   | 161 (54.4)    | 100 (52.9)     | 1.014[0.386-1.714] | 0.325  |
| Female                              | 224 (46.2)   | 135 (45.6)    | 89 (47.1)      | 1            |         |
| Education Level                     |              |               |                |              |         |
| College and above                   | 155 (32)     | 77 (26)       | 78 (41.3)      | 0.713[0.431-0.950] | 0.017* |
| High school and below               | 330 (68)     | 219 (74)      | 111 (58.7)     | 1            |         |
| Place of residence                  |              |               |                |              |         |
| Urban                               | 194 (40)     | 114 (38.5)    | 80 (42.3)      | 2.192[0.689-5.237] | 0.189  |
| Rural                               | 291 (60)     | 182 (61.5)    | 109 (57.7)     | 1            |         |
| Family income ¥Yuan/ M              |              |               |                |              |         |
| □10000                              | 56 (11.5)    | 35 (11.8)     | 21 (11.1)      | 1.885[0.332-6.457] | 0.846  |
| 5001-10000                          | 227 (46.8)   | 133 (44.9)    | 94 (49.7)      | 0.912[0.420-1.518] | 0.092  |
| 3001-5000                           | 175 (36.1)   | 113 (38.2)    | 62 (32.8)      | 3.817[0.774-9.220] | 0.332  |
| □3000                               | 27 (5.6)     | 15 (5.1)      | 12 (6.3)       | 1            |         |
| Primary cancer                      |              |               |                |              |         |
| Lung                                | 122 (25.2)   | 88 (29.7)     | 34 (18)        | 3.892[1.521-10.109] | 0.008**|
| Renal                               | 86 (17.7)    | 59 (19.9)     | 27 (14.3)      | 1.732[0.458-6.256] | 0.122  |
| Gastric                             | 49 (10.1)    | 22 (7.4)      | 27 (14.3)      | 3.069[1.746-9.961] | 0.007**|
| Colorectal                          | 53 (11.3)    | 23 (8.8)      | 30 (14.3)      | 3.549[1.472-9.773] | 0.006**|
|                           | (7.8) | (15.9) | 9.135 |       |
|---------------------------|-------|--------|-------|-------|
| **Breast**                | 89 (18.4) | 59 (19.9) | 30 (15.9) | 1.776 [0.753-3.158] | 0.084 |
| **Non-Hodgkin's Lymphoma**| 56 (11.5) | 34 (11.6) | 22 (11.6) | 4.711 [0.843-7.953] | 0.569 |
| **Others**                | 30 (6.2) | 11 (3.7) | 19 (10) | 1     |
| **Medical insurance**     |       |        |       |       |
| Yes                       | 383 (79) | 231 (78) | 152 (80.4) | 3.791 [0.654-7.824] | 0.264 |
| No                        | 102 (21) | 65 (22) | 37 (19.6) | 1     |
| **CCI**                   |       |        |       |       |
| ≤2                        | 240 (49.5) | 178 (60.1) | 62 (32.8) | 4.139 [1.418-7.027] | 0.003 ** |
| ≤2                        | 245 (50.5) | 118 (39.9) | 127 (67.2) | 1     |
| **Duration of medicine**  |       |        |       |       |
| ≤3                        | 262 (54) | 98 (33.1) | 164 (62.1) | 0.647 [0.463-0.815] | 0.004 ** |
| ≥3                        | 223 (46) | 198 (66.9) | 25 (37.9) | 1     |
| **Combination of medicine**|   |       |       |       |
| Yes                       | 286 (59) | 201 (67.9) | 85 (45) | 1.736 [1.486-4.153] | 0.028  |
| No                        | 199 (41) | 95 (32.1) | 104 (55) | 1     |
| **Route of administration**|       |        |       |       |
| Intravenous               | 209 (43.1) | 164 (55.4) | 45 (23.8) | 3.128 [2.066-7.550] | 0.007 ** |
| Oral                      | 179 (36.9) | 100 (33.8) | 79 (41.8) | 1.806 [0.538-6.872] | 0.075  |
| Others                    | 97 (20)  | 32 (10.8) | 65 (34.3) | 1     |

Abbreviations: ADR, adverse reactions; CCI, Charlson Comorbidity Index

# Unmarried= single, divorced, and widow;

* P values are statistically significant.

a Binary logistic regression models were computed for each characteristic separately and the ADR was included as an independent variable.

*P<0.05, **P<0.01
Table 2 Demographic and disease-related characteristics predicting ADR (multivariate logistic regression)

| Factors          | B estimates | OR     | 95% CI       | P value |
|------------------|-------------|--------|--------------|---------|
| Age              | 0.842       | 1.769  | 1.248-1.728  | 0.022*  |
| Education level  | -0.624      | 0.724  | 0.576-0.962  | 0.036*  |
| CCI              | 0.910       | 1.715  | 1.021-1.824  | 0.021*  |
| Duration of medicine | 0.766   | 1.694  | 1.094-1.743  | 0.022*  |
| Combination of medicine | 0.734   | 1.488  | 1.427-1.655  | 0.033*  |
| Route of administration | 0.689   | 1.652  | 1.468-3.935  | 0.019*  |

(multivariate logistic regression)

Abbreviations: ADR, adverse reactions; CCI, Charlson Comorbidity Index; OR, Odds ratio; CI, Confidence interval;

a The reference categories were age, education level, CCI, duration of medicine, combined treatment and route of administration respectively.

*P<0.05

Table 3 Characteristics of ADR
| Type of ADR                        | Frequency | %     | ADR grading | Frequency | %     |
|-----------------------------------|-----------|-------|-------------|-----------|-------|
| Skin and its accessories          | 125       | 19.3  | Grade 2     | 248       | 38.4  |
| Fatigue                           | 109       | 16.9  | Grade 1     | 153       | 23.7  |
| Mucosal damage                    | 94        | 14.6  | Grade 1     | 143       | 22.1  |
| HBP                               | 76        | 11.8  | Grade 1     | 70        | 10.8  |
| Gastrointestinal discomfort       | 69        | 10.7  | Grade 1     | 32        | 5.0   |
| Insomnia                          | 59        | 9.1   |             |           |       |
| Hand-foot syndrome                | 45        | 7.0   | 1M          | 314       | 51.5  |
| Cardiotoxicity                    | 24        | 3.7   | 1M          | 40.4      |       |
| Hematological system disorders    | 23        | 3.6   | 3M          | 21.2      |       |
| Thrombus                          | 8         | 1.2   | 6M          | 7.0       |       |
| Interstitial pneumonia            | 4         | 0.6   |             |           |       |
| Others                            | 10        | 1.5   |             |           |       |

**The start time of ADR**

| Duration | Frequency | %     |
|----------|-----------|-------|
| 1M       | 333       | 51.5  |
| 1M±      | 264       | 40.9  |
| 3M±      | 49        | 7.6   |

Table 4 Treatment compliance, disease progress and survival according to ADR

| Outcomes                  | B estimates | OR   | 95% CI        | P value |
|---------------------------|-------------|------|---------------|---------|
| Discontinuing medication  | -1.192      | 0.522| 0.384, 0.866  | 0.025*  |
| Change medicine           | -1.887      | 0.438| 0.301, 0.748  | 0.010*  |
| Adjust dosage             | -1.853      | 0.604| 0.473, 0.958  | 0.019*  |
| Take medicine on time     | 1.914       | 1.641| 1.519, 1.799  | 0.022*  |
| Recurrence                | -1.799      | 0.522| 0.285, 0.807  | 0.027*  |
| Metastasis                | -1.805      | 0.630| 0.379, 0.827  | 0.009*  |
| Death                     | -0.562      | 0.881| 0.638, 1.296  | 0.883   |
Abbreviations: ADR, adverse reactions; OR, odds ratio; CI, confidence interval; A binary logistic regression models were computed for each outcome separately; ADR was included as an independent variable, each model was adjusted by age, gender, education level, place of residence, family income, primary cancer, medical insurance, CCI, duration of medicine, combination of medicine and route of administration.

*P < 0.05