



## Off-Label and Off-NCCN Guidelines Uses of Antineoplastic Drugs in China

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### Abstract

**Background:** To evaluate off-label and off-NCCN guidelines uses of antineoplastic drugs in a major Chinese hospital.

**Methods:** Totally 1122 patients were selected from July to December 2011. Then, the off-label and off-NCCN guidelines uses of antineoplastic drugs were analyzed.

**Results:** In 798 of 1122 patients (71.12%), drugs were used for off-label. In 317 of 1122 patients (28.25%), the drugs were prescribed for off-label and off-NCCN guidelines. 2591 medical orders for 1122 patients, 1051/2591 (40.56%) medical orders were off-label; 445/2591 (17.17%) medical orders were off-label and off-NCCN guidelines. In 445 off-label and off-NCCN medical orders, 399 (89.66%) were unapproved indications, 38 (8.54%) were unapproved drug concentration and 12 (2.70%) were unapproved route of administration. Percentage of off-label and off-NCCN guidelines drug uses in male was higher than that in female (21.92% vs. 11.39%,  $P < 0.01$ ). Compared with other lines of treatment, percentage of off-label and off-NCCN guidelines drug uses in postoperative adjuvant was the smallest ( $P < 0.01$ ) and percentage in three or multi-line treatments was the highest ( $P < 0.01$ ). The pancreatic cancer possessed the highest percentage (38.74%) of off-label and off-NCCN guidelines drug uses among all types of cancer ( $P < 0.01$ ).

**Conclusion:** Off-label uses of antineoplastic drugs are generally common in China hospitals based on NCCN guidelines. The fact suggests that anti-tumor treatment was relatively standard in China. Off-label and off-NCCN guidelines drug uses were mainly for individual treatment. Doctors should fully consider the adverse drug reaction, contraindication, cautions and increase the drug security monitoring. Uncorrected drug concentration should be avoided for drug risk.

**Keywords:** Antineoplastic drug use, Off-label and off-NCCN guidelines, China

### Introduction

Any new drug labeled for an indication, dose and route of administration by drug approval authorities is on-label. Use of a drug outside the terms of its official labeling is referred to as off-label (1). Off-label prescription is common in medical practice, especially in oncology where drugs are often prescribed off-label (2-7). It is mainly because effective approved drugs are scarce. In addition, many widespread anticancer drugs have not gained the label for all the indications under which

they can be effectively employed. The pressure from patients, who require in any case treatment for their disease, is another main reason for off-label prescriptions in China. Last but not least, the rapid diffusion of preliminary results of clinical trials and the lagged approval of new drugs (or extension of indications of drugs already approved) by the European Medicines Agency and the US Food and Drug Administration (FDA) are another potential important reasons for off-label

prescriptions (8,9). Antineoplastic drugs could lead to possible health, legal and economic problems without instruction supports due to the potential high toxic effects, narrow safety scope and high price. However, few data are available on the incidence of off-label use of antineoplastic drugs (4, 10). In 2004, Susan and Michael assessed that 22% of the prescriptions were either off-label or unlicensed at Peter MacCallum Cancer Centre, Australia (6). A recent estimation by the National Comprehensive Cancer Network (NCCN) calculated that 50-75% uses of all drugs in cancer care in the United State were off-label (11). A large study conducted in the USA revealed that 33.2% of chemotherapy was off-label (12). An Australia survey assessed that a total of 448 protocols contained 82 different drugs across 15 tumor groups. Overall, 189 (42.2%) of protocols were off-label, and three (0.7%) were unlicensed (13). An Italian prospective, observational, multicenter survey revealed that off-label use of antineoplastic drugs represented less than 20% of the prescriptions and most of them were based on scientific evidences of efficacy (14).

In China, leaflet is the legal document to deal with medical dispute and there is no clear legislation for drug uses beyond labels. NCCN guidelines sponsored and formulated by the 21 top American cancer centers were widely recognized by global community of tumor circles. The NCCN guidelines document is evidence-based and consensus-driven, ensuring that all patients receive preventive, diagnostic treatment and supportive services for the optimal outcomes. Currently, the NCCN guidelines document has been the first-hand reference material for cancer treatment since its introduction to China in 2005.

There was only one research involving antineoplastic drug uses based on the specifications and NCCN guidelines. The survey on prescribing practices of 10 important drugs used for cancer was conducted in March 2010 in India, in which off-label use was further evaluated by NCCN guidelines (15). To date, there was no relevant research data about antineoplastic drug uses according to the specifications or/and NCCN guidelines in China. The Chinese people's liberation army

general hospital is the largest comprehensive hospital in China, owning more than 4400 beds in all and more than 200 beds in oncology.

The purpose of this study was to survey the off-label and off-NCCN guidelines uses of antineoplastic drugs in the Chinese people's liberation army general hospital and to understand the actual antineoplastic drug uses in China.

## Materials and Methods

All discharged patients in department of oncology were selected from July to December for a randomized week every month in 2011 with the Hospital Information System of the Chinese people's liberation army general hospital. One thousand one hundred and twenty-two of 1307 (85.84%) patients were submitted to chemotherapy. Except clinical trial drugs, all antitumor drugs were included in this study.

According to the latest drug leaflet approved by China's State Food and Drug Administration, the indications (treatment lines, types of cancer and drug combination), drug preparation (solvent and concentration) and route of administration were analyzed. Off-label use was further evaluated with the NCCN guidelines version 1.2011 (including Chinese NCCN version 1.2011) to determine medical orders off the leaflet and NCCN guidelines. The doses of antitumor drugs were not enrolled because they were probably to adjust based on their toxic and specification factors, while some overdoses medical orders would be explained in discussion. Each off-label and off-NCCN guidelines medical order was counted once. Meanwhile, different categorizations on one medical order were needed to count alone. The data were analyzed with the chi square test and statistical software SPSS version 13.0 with test level  $\alpha=0.05$ . *P* values less than 0.05 were considered statistically significant.

## Results

One thousand one hundred and twenty-two patients were chosen under the defined conditions (Table 1).

**Table 1:** Characteristics of 1122 patients submitted for chemotherapy

Characteristic	No.	%
<b>Sex</b>		
Female	528	47.06
Male	594	52.94
<b>Age (yr)</b>		
<50	477	42.51
50~64	518	46.17
≥65	127	11.32
<b>Treatment lines</b>		
Postoperative auxiliary	371	33.06
First line	510	45.45
Second line	90	8.02
Third and multi line	79	7.04
Others §	72	6.42
<b>Types of cancer</b>		
Lung	301	26.83
Breast	204	18.18
Colorectal	187	16.67
Gastric	156	13.90
Pancreatic	49	4.37
Head& neck	42	3.74
Esophageal r	36	3.21
Neuroendocrine	29	2.58
Ovarian	24	2.14
Hepatobiliary	19	1.69
Others	75	6.68

§ Others include neoadjuvant chemotherapy, first line maintenance, second line maintenance and multi line maintenance.

In 798 of 1122 patients (71.12%), the drugs were used for off-label. In 317 of 1122 patients (28.25%), the drugs were prescribed for off-label and off-NCCN guidelines. In 2591 medical orders for 1122 patients, 1051/2591 (40.56%) medical orders were off-label and 445/2591 (17.17%) medical orders were off-label and off-NCCN guidelines, covering such aspects as unapproved indications, unapproved drug concentration and unapproved route of administration. There were four off-label and off-NCCN medical orders in two aspects. Three hundred and ninety-nine of 445 (89.66%) medical orders were unapproved indication, accounting for the largest percentage. Thirty-eight of 445 (8.54%) medical orders were unapproved drug concentration. For example, concentration of gemcitabine was more than 40

mg/mL, which was forbidden by leaflet; concentration of paclitaxel was lower than 0.3mg/mL in contrast with concentration of 0.3-1.2 mg/mL demanded by leaflet. In some medical order, the concentration of etoposide, which cannot exceed 0.25 mg/mL according to the leaflet, reached 0.8mg/mL. Twelve of 445 (2.70%) medical orders involved the unapproved route of administration. For instance, nimotuzumab, pemetrexed and cisplatin were administered for spinal canal injection; gemcitabine and pemetrexed were administered for thoracic injection; rh-endostatin was administered for intraperitoneal injection. All of above route administration were forbidden in the leaflet (Table 2).

**Table 2:** Categorization of off-label and off-NCCN guidelines medical orders in 1122 patients

Categorization	No.	%
Unapproved indication	399	89.66
Unapproved treatment lines	88	
Unapproved types of cancer	182	
Unapproved combination	129	
Unapproved drug concentration	38	8.54
Unapproved route of administration	12	2.7
Unapproved spinal canal injection	6	
Unapproved chest injection	3	
Unapproved intraperitoneal injection	3	

The following data were analyzed by the chi-square test, showing that sex, treatment lines and tumor types were statistically significant in off-label and off-NCCN guidelines uses ( $P<0.01$ ) (Table 3). Percentage of off-label and off-NCCN guidelines drug uses in male was higher than that in female (21.92% vs. 11.39%,  $P<0.01$ ). Compared with other lines of treatment, percentage of off-label and off-NCCN guidelines drug uses was the smallest in postoperative adjuvant ( $P<0.01$ ). Percentage of off-label and off-NCCN guidelines drug uses was highest in three or multi-line treatments ( $P<0.01$ ). Compared with other tumors, pancreatic cancer possessed higher percentage (38.74%) of off-label and off-NCCN guidelines drug uses ( $P<0.01$ ). Antineoplastic drugs for off-label and off-NCCN guidelines were ranked according to numbers of medical orders.

**Table 3:** Off-label and off-NCCN medical orders used on different sex, age, treatment lines and types of cancer

Categorization	No. of off-label and off-NCCN medical orders	No. of on-label and on-NCCN medical orders	Total	%	<i>P</i>
<b>Sex</b>					
Female	133	1035	1168	11.39	<0.01
Male	312	1111	1423	21.92	
<b>Age, yr</b>					
<50	198	946	1144	17.31	>0.05
50~64	204	968	1172	17.41	
≥65	43	232	275	15.64	
<b>Treatment lines</b>					
Third and multi line	42	79	121	34.71	<0.01
Second line	31	125	156	19.87	
Postoperative auxiliary	112	781	893	12.54	
First line	239	1018	1257	19.01	
Others	31	132	163	19.02	
<b>Types of cancer</b>					
Colorectal	88	535	623	14.12	<0.01
Lung	74	445	519	14.26	
Gastric	120	342	462	25.97	
Head and Neck	30	87	117	25.64	
Breast	23	373	396	5.81	
Pancreatic	43	68	111	38.74	
Esophageal	10	57	67	14.93	
Ovarian	9	40	49	18.37	
Neuroendocrine	14	52	66	21.21	
Hepatobiliary	4	32	36	11.11	
Others	30	115	145	20.69	

The top three drugs in turn were docetaxel, oxaliplatin and capecitabine. Docetaxel was used for unapproved timing, unapproved combination and unapproved types of cancer (Table 4). For instance, DCF chemotherapy was used for first-line treatment of gastric cancer, not for postoperative adjuvant chemotherapy recommended by NCCN guidelines. Docetaxel was associated with rh-endostatin for treatment of advanced gastric cancer (while docetaxel was not recommended for this combination in NCCN guidelines). Docetaxel was also prescribed to treat the thymus gland tumor and hepatobiliary cancer, not being approved in the leaflet and NCCN. In addition, molecular targeted drugs were ranked the fifth in the top 10 of drugs. Although many clinical studies about molecular targeted drugs were in progress for a relatively short research and

development time, the molecular targeted drugs were still widely used due to good effect and little adverse reaction, thus accounting for a higher proportion in for off-label and off-NCCN guidelines cases.

Antitumor drugs such as nimotuzumab, oxaliplatin and rh-endostatin were widely used in all kinds of unapproved cancer treatment (Table 5). The indication of nimotuzumab in association with radiotherapy recommended by the leaflet and NCCN was stage **III/IV** nasopharyngeal carcinoma when epidermal growth factor receptor (EGFR) expressed positive. Nimotuzumab was widely applied in other types of cancer patients for its action mechanism was similar to cetuximab and its allergic reaction was less than that of cetuximab with complete humanization. Rh-endostatin, a new antiangiogenic drug manufactured by China

and only for treatment of non-small cell lung cancer (NSCLC) recommend by the leaflet and Chinese NCCN, was also widely used in clinic. Gefitinib was used for treatment of pulmonary

metastasis of the colon, mixture of small cell lung cancer (SCLC) and possible adenocarcinoma, unknown primary tumor and pancreatic cancer.

**Table 4:** The top 10 off-label and off-NCCN guidelines antineoplastic drugs

Rank	Drug	No. of medical orders	Classification of the off-label and off- NCCN guidelines (numbers of medical orders)
1	Docetaxel	78	treatment lines 42 combination 30
2	Nimotuzumab	55	type of cancer types6 type of cancer 52
3	Oxaliplatin	54	route of administration3 treatment lines5 combination 23
4	Capecitabine	48	type of cancer 26 treatment lines6 combination 35
5	Rh-Endostatin	35	type of cancer 7 combination 3 type of cancer 30
6	Erlotinib	29	route of administration 2 treatment lines10 combination 15
7	Gefitinib	26	type of cancer 4 treatment lines6 combination 4
8	Bevacizumab	24	type of cancer 16 treatment lines4 combination 10
9	Etoposide	23	type of cancer 10 concentration23
10	Pemetrexed	21	combination 6 type of cancer 12 route of administration3

In inappropriate treatment lines, docetaxel ranked No.1. For instance, it was used for postoperative adjuvant chemotherapy of gastric cancer, first line treatment of cervical cancer and SCLC. Erlotinib ranked No.2 and was used for the postoperative adjuvant, first line without EGFR mutation detection and multi line chemotherapy of NSCLC. Gefitinib ranked No.3 and was used for the postoperative adjuvant, first line without EGFR mutation detection of NSCLC. Capecitabine was applied for the postoperative adjuvant treatment of stage I and multi line chemotherapy of colorectal cancer. Oxaliplatin was used for the postoperative

adjuvant chemotherapy of stage I, stage II A (without risk factors) of colon cancer and multi-line chemotherapy of colorectal cancer (Table 5). The top five drugs with inappropriate combination uses, were capecitabine, docetaxel, oxaliplatin, erlotinib and bevacizumab. For instance, combination of capecitabine with docetaxel was used for postoperative adjuvant treatment of gastric cancer (capecitabine, not being registered in leaflet, was recommended by NCCN to combine with oxaliplatin by NCCN).Combination cetuximab with oxaliplatin and capecitabine, had been deleted from NCCN guidelines since 2010 (Table 5).

**Table 5:** Description of off-label and off-NCCN guidelines antineoplastic drugs

	Rank	Drugs	No. of medical orders
The top five anti-neoplastic drugs on cancer types	1	Nimotuzumab	52
	2	Rh-endostatin	30
	3	Oxaliplatin	26
	4	Gefitinib	16
	5	Pemetrexed	12
The top five anti-neoplastic drugs on treatment lines	1	Docetaxel	42
	2	Erlotinib	10
	3	Gefitinib	6
	4	Capecitabine	6
	5	Oxaliplatin	5
The top five anti-neoplastic drugs on combination	1	Capecitabine	35
	2	Docetaxel	30
	3	Oxaliplatin	23
	4	Erlotinib	15
	5	Bevacizumab	10

## Discussion

In the Chinese people's liberation army general hospital, 1051/2591 (40.56%) medical orders were off-label and 445/2591 (17.17%) medical orders were off-label and off-NCCN. The fact suggests that off-label uses of antineoplastic drugs were common, while most anticancer drug applications followed the evidence of Cochrane in China and therapeutic schedules were relatively standard. The off-label or off-NCCN drug uses in female were less than that in male ( $P < 0.01$ ), considering that most women suffered from breast cancer in which therapeutic schedules were more various and standard. Compared with other lines of treatment, three or multi-line treatments possessed the highest percentage of off-label and off-NCCN guidelines cases ( $P < 0.01$ ). The clinical trials or best supportive care were recommended in three or multi-line treatment of NCCN, while Chinese doctors kept on empirical treatment with patients' requests. Compared with other tumors, pancreatic cancer possessed higher percentage (38.74%) of off-label and off-NCCN guidelines cases ( $P < 0.01$ ), due to combination of nimotuzumab and other targeted drugs to try high efficacy for poor therapeutic effect in pancreatic cancer (16-18). Although there were no clinical research data to support some off-label and off-NCCN guidelines

drugs such as nimotuzumab for brain metastases patients with intrathecal injection, good therapeutic effect was indeed acquired in some patients. Moreover, there was some research for the use of other targeted drugs such as intrathecal rituximab and trastuzumab (19,20). Some NSCLC patients treated with gefitinib or erlotinib were subjected with double doses to overcome drug resistance or achieved a higher cerebrospinal fluid concentration. It occurred when no other good treatment options were available. In addition, the patients were requested to sign the informed consent. The use of high dose gefitinib or erlotinib was also reported in previous reports (21-23). Although some off-label and off-NCCN uses were for the individual treatment, doctors should fully consider adverse drug reactions, contraindications, cautions and increase the drug security monitoring when lacking clinical research data. It has been demonstrated that patients exposed to off-label drug use are at a higher risk of adverse drug effects (24,25). Uncorrected drug concentration should be avoided for drug risk in some off-label drug uses.

Some important limitations were presented in this study, such as the scarce number of patients evaluated, which contrasts with the large variability induced by the variety of the type of neoplasm, of chemotherapeutic schemes, of antineoplastic

drugs used, etc. Meanwhile, the doses of antitumor drug were not enrolled due to difficult evaluation. Precisely, because some of the different identified categories are not mutually exclusive and the choice of prevalence criteria to classify each one of them possesses a component of arbitrariness. In addition, analysis data was only from one hospital and only from department of oncology. All these limitations suggest that further multi-center research was needed in the future.

## Conclusion

Off-label uses of antineoplastic drugs are generally common in China hospitals based on NCCN guidelines. The fact suggests that anti-tumor treatment was relatively standard in China.

## Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc) have been completely observed by the authors.

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