

Off-label prescription of antineoplastic drugs: an Italian prospective, observational, multicenter survey

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ABSTRACT

Aims and background. An appropriate use of drugs should follow the registered indications. Different reasons can induce oncologists to prescribe drugs off-label. The aim of this study was to describe incidence and characteristics of these prescriptions in Italy.

Methods. Patients submitted to chemotherapy in 15 Italian oncology centers were evaluated for two randomized non-consecutive days of two weeks in May 2006.

Results. The study enrolled 644 patients receiving 1,053 drugs. Overall, 199 of 1053 (18.9%) prescriptions were off-label. In 92 of 199 cases (46.2%), the drugs were used for a neoplasm for which they were not approved, but there was scientific evidence (one or more randomized clinical trials or more phase II studies published in a major oncology journal) justifying the prescription. In 27 cases (13.6%), the drugs were prescribed for a rare neoplasm (cisplatin and gemcitabine in mesothelioma). In 20/21 cases (10.1%/10.5%), drugs were used in association/alone in contrast with the approved use (capecitabine in association in colorectal cancer). In 28/11 cases (14.0%/5.6%), the drugs were used in lines of chemotherapy subsequent/previous to that approved.

Conclusions. Off-label use of antineoplastic drugs, in this observational survey, represents less than 20% of the prescriptions, and most of them are based on scientific evidence of efficacy.

Introduction

An appropriate use of antineoplastic drugs, essential to reproduce in daily clinical practice the results achieved in clinical trials, should follow the registered indications at the approved doses. However, when drugs are used in clinical practice, there is a natural trend to extend their utilization to certain patient categories, for example to the elderly or to children, for which there is no evidence of efficacy or tolerability documented by randomized clinical trials. Especially in oncology, drugs are often prescribed off-label for other reasons^{1,2}. Among these are lack of precision in the indications of some of the oldest drugs (i.e., cyclophosphamide has been approved as a "cytostatic treatment") or in the case of rare tumors, for which the documentation of activity, efficacy and tolerability is generally scarce so that often there are no drugs approved for such indications. Pressure from patients, who require in any case treat-

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ment for their disease, is another reason for off-label prescriptions. Last but not least, the rapid diffusion of preliminary results of clinical trials and the late approval of new drugs (or extension of indications of drugs already approved) by the European Medicines Agency with respect to the US Food and Drug Administration (FDA) are other potential important reasons for off-label prescriptions^{3,4}.

It is clear that the off-label utilization of an anticancer drug could determine possible health problems due to the potential toxic effects of the drug and to the frequent lack of efficacy data, legal problems for the physicians prescribing off-label drugs, and economic problems for the National Health Service.

Few data are available on the incidence of off-label prescriptions. A 2001 national survey of USA office-based physicians showed that 150 million prescriptions (21%) were for off-label use. The phenomenon was more common among cardiac medications and anti-convulsants. More important was the fact that 73% of off-label prescriptions had little or no scientific support⁵.

This could be the consequence of the 1997 FDA Modernization Act, which allowed pharmaceutical companies to disseminate articles from peer-reviewed journals about off-label use⁶. According to the Act, such changes were to allow physicians to make more informed prescribing decisions and to motivate pharmaceutical companies to do the clinical studies necessary to get these indications added to drug labeling.

A recent estimate by the National Comprehensive Cancer network calculated that 50-75% of all uses of drugs in cancer care in the United States are off-label⁵. Furthermore, approximately 90% of patients with rare diseases are given at least one drug that is off-label⁶, and three fourths of the prescriptions on the market do not have labeling indications for children⁷⁻⁹.

A survey carried out in 1991 on 681 members of the American Society of Clinical Oncology showed that almost all drugs were prescribed for off-label use at least once, and that all types of cancer examined were treated with some drugs that were prescribed for off-label use. One third of the over 5,000 drug administrations were given for off-label use, and over half (56%) of the patients received at least one drug of their treatment regimen that was prescribed for off-label use. In general, off-label use was higher in those cases where there was no agreement on the best therapy, higher in patients treated with a palliative intent than with a curative intent, and higher in patients with metastasized cancer than in those with cancer at early stages of development¹⁰.

More recently, an Australian study prospectively evaluated the medication charts of a single day of 130 cancer patients hospitalized in January 2001¹¹. Among 1351 prescriptions, 293 (22%) were off-label and 85% of patients received at least one drug off-label.

In 2006 the Italian Association of Medical Oncologist (AIOM) planned and supported a survey to verify the real incidence and characteristics of off-label prescriptions in Italian oncological centers.

Materials and methods

The study was proposed by e-mail to 386 Italian oncology institutions. No recall procedure was made nor was there any check of receipt. Reasons for nonacceptance were not collected.

The protocol planned that all consecutive patients submitted to cancer chemotherapy during two days selected at random were asked to participate in the study. To avoid the same patient being invited twice, randomization was conditioned so that the two days assigned to each participating center had to fall in two different and consecutive weeks and that the two days had to be different. Patients submitted only to supportive/palliative care and patients refusing to participate in the study for any reason were excluded. The study was approved by the local ethics committee. The investigators filled out a form reporting patient data (age, sex, ECOG performance status, type and stage of cancer) and the type of chemotherapy received during the current visit to the center or in a previous visit.

Descriptive analysis was done initially considering each drug as a unit. Before data computerization, it was decided that each single administered drug should be categorized within one of five categories:

- 1) used appropriately, according to registration;
- 2) used for a non-rare cancer for which the drug is not registered;
- 3) used for a rare cancer (defined as a cancer with a prevalence of 50/100,000) for which the drug is not registered;
- 4) used with inappropriate combination, including two subcategories: a) used in association with other drugs for drugs registered as single agents, b) used as single agents for drugs registered in association;
- 5) used with inappropriate timing, including two subcategories: a) used before the line of treatment for which the drug is registered, b) used after the line of treatment for which the drug is registered.

A hierarchical criterion of classification was adopted (in the order reported above). Therefore, categories were mutually exclusive except for points 4 and 5, for which a drug could have been used with inappropriate combination and inappropriate timing (Table 1). Registration status of each drug in Italy was considered at the time of the data collection (May 2006).

Finally, an analysis that considered each patient as a unit was performed in order to describe the appropriateness of the use of drug combinations, frequently used in oncology.

Table 1 - Categories of prescription

In-label prescription no. (%)	854/1053 (81.1)
Off-label prescription, no. (%)	199/1053 (18.9)
1. Different cancer	92 (46.2%)
2. Different timing	
Used earlier	11 (5.6%)
Used in subsequent lines	28 (14.0%)
3. Rare neoplasia	27 (13.6%)
4. Inappropriate combination	
Used in association while registered as single agent*	20 (10.1%)
Used as single agent while registered in association [§]	21 (10.5%)

*In 4/20 patients, capecitabine, used in combination while registered as a single agent, was also used after it was indicated.

§In 1/21 patients, cetuximab, used as a single agent while registered in association with irinotecan, was also used before it was indicated.

Results

Fifteen institutions (8 in the north, 3 in the center, and 4 in the south of Italy) agreed to participate in the study, which was conducted during the month of May 2006, enrolling an overall number of 644 patients. As can be observed in Table 2, patients were mostly females, older than 50 years and with a good performance status; cancer was metastatic in about two-thirds of the cases; breast and colorectal cancer accounted for more than 50% of the cases.

Table 2 - Characteristics of 644 patients

Characteristic	No.	%
Sex		
Females	358	55.6
Males	282	43.8
Not specified	4	0.6
Age, yr		
<50	127	19.7
50-64	250	38.8
≥65	263	40.8
Not specified	4	0.6
Performance status (ECOG)		
0	430	66.8
1	151	23.4
2	23	3.6
3	6	0.9
Not specified	34	5.3
Presence of metastatic disease		
No	240	(37.3)
Yes	404	(62.7)
Type of cancer		
Breast	206	32.0
Colorectal	143	22.2
Lung	85	13.2
Gastric	27	4.2
Ovarian	24	3.7
Head & neck	20	3.1
Bladder	19	3.0
Other	120	18.6

Classification of prescriptions according to the proposed scheme are reported in Table 1. Overall, 199/1053 (18.9%) prescriptions were off-label for at least one reason.

In 92 of 199 prescriptions (46.2%), the drugs were used on a neoplasm for which they were not approved (Table 3).

In 27 patients (13.6%), the drugs were prescribed for a rare neoplasm (i.e., fluorouracil and mitomycin in anal cancer, and cisplatin and gemcitabine in mesothelioma and biliary tree cancer) (Table 4).

In 21 patients (10.5%), the drugs were used alone despite the fact they were approved only in association (gemcitabine in breast and ovarian cancer, paclitaxel, docetaxel and liposomal doxorubicin in breast cancer) (Table 5). Finally, 20 colorectal cancer patients (10.1%) were treated with capecitabine in association with other antineoplastic agents while the drug was approved for use as a single agent (Table 5).

Table 3 - Description of off-label prescriptions due to type of cancer

Drug	Type of cancer	No. of prescriptions
5-Fluorouracil	Esophageal	1
Gemcitabine	Small cell lung	2
Cisplatin	Breast	2
	Melanoma	2
	Pancreas	1
	Stomach	6
Oxaliplatin	Esophageal	1
	Stomach	1
	Pancreas	4
	Unknown primary	1
Paclitaxel	Cervix	2
	Endometrial	3
	Small cell lung	5
Carboplatin	Endometrial	3
	Breast	8
	Non-small cell lung	10
	Bladder	4
Capecitabine	Pancreas	2
	Stomach	1
	Unknown primary	1
Epirubicin	Endometrial	3
Irinotecan	Small cell lung	2
	Stomach	3
Docetaxel	Stomach	1
	Head & neck	2
	Ovarian	1
Cladribine	Non-Hodgkin lymphoma	4
Fludarabine	Non-Hodgkin lymphoma	2
Ifosfamide	Small cell lung	1
Methotrexate	Bladder	1
Topotecan	Small cell lung	2
Vinblastine	Renal	1
	Melanoma	1
Vinorelbine	Small cell lung	1
	Head & neck	2
Etoposide	Ovarian	1
	Endometrial	3
	Non-small cell lung	1

Table 4 - Drugs used for rare neoplasms

Drug	Type of cancer	No. of prescriptions
Gemcitabine	Biliary tree	6
	Pleural	2
	Sarcoma	1
	Testicular	1
Cisplatin	Biliary tree	3
	Pleural	1
Etoposide	Testicular	3
	Ovarian non-epithelial	1
5-Fluorouracil	Anal	1
Mitomycin C	Anal	1
Oxaliplatin	Peritoneal carcinomatosis	1
	Biliary tree	1
Paclitaxel	Testicular	1
	Thymus	1
Carboplatin	Thymus	1
Epirubicin	Biliary tree	1
Tomudex	Peritoneal carcinomatosis	1

Table 5 - Drugs used alone or in combination but approved differently

Group and drug	Type of cancer	No. of prescriptions
Prescribed alone but approved in combination		
Docetaxel	Breast	9
Gemcitabine	Breast	5
	Ovarian	2
Paclitaxel	Breast	2
Cetuximab	Colorectal	2
Lyposomal doxorubicin	Breast	1
Prescribed in combination but approved alone		
Capecitabine	Colorectal	20

Thirty-nine prescriptions were inappropriate because of their timing.

In 11 patients (5.6%), the drugs were used in lines of chemotherapy previous to that approved (i.e., paclitaxel, trastuzumab and capecitabine as first line for breast cancer and cetuximab as first line for colorectal cancer) (Table 6). In 28 patients (14%), the drugs were used in lines of chemotherapy subsequent to that approved (i.e., oxaliplatin and capecitabine as second and subsequent lines in colorectal cancer, paclitaxel in breast cancer, irinotecan combined with folinic acid and fluorouracil in colorectal cancer, bevacizumab as second line in colorectal cancer) (Table 6).

In the study, 246 patients received a single drug and 398 a combination of two or more antineoplastic agents. The prescription of 172 of 398 schemes of chemotherapy (43%) was not consistent with registration; details are reported in Table 7). In 92 combinations (54%), one or more drugs were not registered for the use that was being made of them. In 54 combinations (31%), the drugs were approved singularly but not associated; among

Table 6 - Drugs used for lines of treatment different from that for which they are registered

Group and drug	Type of cancer	No. of prescriptions
Prescribed after the line for which it is registered		
Irinotecan	Colorectal	13
Oxaliplatin	Colorectal	4
Trastuzumab	Breast	4
Bevacizumab	Colorectal	4
Paclitaxel	Breast	2
Capecitabine	Colorectal	1
Prescribed before the line for which it is registered		
Paclitaxel	Breast	4
Capecitabine	Breast	3
Trastuzumab	Breast	2
Cetuximab	Colorectal	2

Table 7 - Reasons for off-label prescriptions of drugs used in combination (172 patients)

	No. of patients (%)
One or more drugs not approved	92 (54)
Approved but not in combination	54 (31)
Not approved after first line	23 (13)
Not approved as first line	3 (2)

these there were 17 combinations of capecitabine plus oxaliplatin for colorectal cancer (while capecitabine was registered as single agent only), 10 combinations of trastuzumab with vinorelbine, gemcitabine or capecitabine for breast cancer (while trastuzumab was registered only with paclitaxel and docetaxel), 8 combinations of capecitabine plus vinorelbine for breast cancer (capecitabine being registered only with docetaxel), 5 combinations of carboplatin plus paclitaxel for ovarian cancer (paclitaxel registered only with cisplatin). In 23 cases (13%), the combination was used after the line of treatment for which it was approved, including trastuzumab plus docetaxel or paclitaxel for breast cancer patients and irinotecan in different combinations with folinic acid and 5-fluorouracil or with bevacizumab for colorectal cancer. Finally, in 3 cases the combination was used before the line of treatment for which it was approved, including 2 patients who received cetuximab plus irinotecan and one who received cetuximab plus oxaliplatin, folinic acid and fluorouracil for colorectal cancer as first-line chemotherapy (while cetuximab was approved only in patients refractory to irinotecan in combination with irinotecan) (Table 7).

Discussion

The off-label use of antineoplastic agents is an important health, legal and economic problem. To date, few

data are available on off-label prescription, and data of prospectively evaluated off-label prescriptions in several oncology centers are lacking. This survey adds important information about the incidence and the characteristics of off-label prescription. First, off-label use of the single antineoplastic drugs represents less than 20% of the prescriptions, and most of them are based on evidence of efficacy (i.e., one or more randomized clinical trials or more phase II trials published in a major oncology journal) justifying their prescription (Table 3) (i.e., fluorouracil in esophageal cancer, cisplatin in breast and gastric cancer, paclitaxel in endometrial and cervical cancer, carboplatin in non-small cell lung, breast and bladder cancer, epirubicin in endometrial cancer, methotrexate in bladder cancer, topotecan in small cell lung cancer, irinotecan in gastric cancer). Based on the results of the present study, the Italian Drug Agency (AIFA) decided to review evidence supporting the use in clinical practice of many of these antineoplastic agents and then to reimburse them¹².

An apparently superior rate is observed when we consider chemotherapeutic schemes (43%). However, in this case, the evidence for non-approved combinations is strong and, therefore, the true off-label incidence not supported by scientific evidence is even lower. Therefore, the most important conclusion is that off-label prescriptions are limited.

Our study presents some important limitations, 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. Precisely, because some of the different categories identified are not mutually exclusive, and the choice of prevalence criteria to classify each one of them has a component of arbitrariness. Finally, the off-label classification proposed has not been tested for reproducibility and validity. All these limitations suggest that the results should be confirmed by other groups with other studies.

Appendix

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