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GAO

Report to the Chairman, Committee on Labor and Human Resources, U.S. Senate

September 1991

OFF-LABEL DRUGS

Reimbursement Policies Constrain Physicians in Their Choice of Cancer Therapies

GAO/PEMD-91-14

GAO

United States
General Accounting Office
Washington, D.C. 20548

Program Evaluation and
Methodology Division

B-242851

September 27, 1991

The Honorable Edward M. Kennedy
Chairman, Committee on Labor
and Human Resources
United States Senate

Dear Mr. Chairman:

At your request, we have studied the prevalence of off-label use of anticancer drugs; how that use varies by cancer type and patient characteristics; and the extent to which health insurers are denying reimbursement for off-label use. (By "off-label" drug use, we mean the use of drugs approved for one type of cancer to treat other types.)

In February, we published the initial results of our national survey of oncologists (GAO/PEMD-91-12BR, Feb. 25, 1991). We are pleased to forward to you now our detailed analysis of the results of our study.

As agreed with your office, we will send copies to the Secretary of Health and Human Services, Administrator of the Health Care Financing Administration, Commissioner of the Food and Drug Administration, and Director of the National Cancer Institute. We will also send copies to other interested parties upon request.

If you have any questions or would like additional information, please call me at (202) 275-1854 or Robert L. York, Acting Director of Program Evaluation in Human Service Areas, at (202) 275-5885. Other major contributors to this report are listed in appendix IV.

Sincerely yours,

Eleanor Chelimsky
Assistant Comptroller General

Executive Summary

Purpose

The practice of medicine is increasingly constrained by restrictions imposed from many quarters, including patient demands for greater participation, concerns over litigation, and efforts to reduce the high cost of health care. Physicians argue that the treatment of cancer patients is one area where restrictions may be compromising the quality of care. Specifically, oncologists report that health insurers are denying reimbursement for some drugs used "off-label" (that is, using drugs approved for one type of cancer to treat other types). The Senate Committee on Labor and Human Resources asked GAO to examine the issue of off-label drug use in the treatment of cancer. The Committee asked:

- To what extent are approved anticancer drugs prescribed for off-label uses, and how does this vary by patient characteristics, therapeutic intent, and type of cancer?
- To what extent are third-party payers reimbursing physicians for the cost of anticancer drugs when they are prescribed for off-label uses?
- To what extent have physicians altered the way they treat cancer patients because of difficulties in obtaining reimbursement for off-label drug use?

Background

When the Food and Drug Administration (FDA) approves a new drug for marketing, it also approves the label (or package insert) that indicates the clinical conditions for which the drug has been proven safe and effective. Once a drug is approved for marketing, however, physicians can use it in any medically appropriate way and not solely for the "labeled" indication. "Off-label" use refers to instances in which drugs are used to treat conditions other than those included on the label.

Health insurers, citing their responsibility to pay only for medically appropriate care, have increased the scrutiny with which they review claims for reimbursement. They are now questioning certain off-label uses of anticancer drugs, arguing that these uses are "investigational" because the FDA has approved the drugs as effective only for certain "labeled" cancers. In the FDA's view, however, off-label drug use is not necessarily investigational. Further, physicians argue that research conducted after the drug is labeled by the FDA often demonstrates new and improved uses and can serve as sufficient evidence to support reimbursement decisions.

GAO examined the prevalence of off-label drug use through a questionnaire sent to a nationally representative sample of oncologists.[1] The sampling frame allowed GAO to generalize to both the national and the state levels for the 11 states where cancer is most prevalent. The response rate was 56 percent, and an analysis comparing respondents to nonrespondents uncovered no evidence of bias in the sample. (See appendix I.)

Results in Brief

GAO found that off-label use of anticancer drugs is widespread. A third of all drug administrations to cancer patients were off-label, and more than half of the patients received at least one off-label drug. The extent of off-label use varied by therapeutic intent, stage of disease, and type of cancer. In general, off-label use was higher where there was no consensus on the best therapy for a specific cancer.

More than half of the survey respondents reported reimbursement problems for the use of drugs off-label, with most indicating that problems were getting worse. Oncologists reported that, in general, it was difficult for them to keep up with the reimbursement policies of third-party payers. Finally, the extent of problems with reimbursement reported to GAO varied significantly across the 11 states for which generalizable conclusions could be drawn.

Respondents also reported that reimbursement policies and the costs of certain drugs have made them alter their preferred treatments. Most important—because of the high prevalence of the diseases—is GAO's finding that the treatments for lung and colon cancers were among those most influenced by reimbursement policies. Another response GAO received relates to the setting in which oncologists provide care. Some 62 percent of GAO's respondents reported admitting patients to the hospital solely to circumvent restrictions imposed by reimbursement policies. They are doing so because drug reimbursement policies are generally less restrictive for inpatient care.

[1]See Off-Label Drugs: Initial Results of a National Survey (GAO/PEMD-91-12BR, Feb. 25, 1991).

GAO's Analysis

Patterns of Off-Label Drug Use

GAO found that about 25 percent of anticancer drugs were prescribed for off-label uses that were supported in at least one of three drug compendia.[2] Another 9 percent, however, were not cited in these sources. More importantly, GAO found that 56 percent of the cancer patients were given at least one drug off-label, and about a third of them received at least one drug for a treatment not cited in the compendia. The absence of a citation for a drug use may be the result of a research publication lag or the lack of evidence that the drug has efficacy for that use. GAO found no pattern of off-label use by age group and gender.

Reimbursement Experiences

Approximately two thirds of the oncologists reported "moderate" to "very great" difficulties in staying abreast of shifts in reimbursement policy. Sixty percent claimed that there had been a "moderate" to "very great" increase during the previous 12 months in the time it took to receive payments. About half reported having been denied reimbursement for an off-label treatment in the last 12 months, and an additional 19 percent were denied reimbursement, but could not say why. Finally, almost three out of four oncologists reporting reimbursement denials for off-label drug use indicated that the rate of denials had increased.

The problems experienced by oncologists varied by state and by third-party payer. Between 31 and 66 percent of respondents from the 11 states for which generalizable conclusions can be drawn reported reimbursement denials for off-label drug use in the last 12 months. Further, at least one oncologist in 19 states reported that because of reimbursement policies therapies had to be changed for patients who had moved from other states. The third-party payers most frequently cited by oncologists as causing them to alter their preferred treatments were Medicare claims-processing contractors. This is not surprising, as most cancer patients are elderly and covered by Medicare. GAO found no relationship between the costs of a drug regimen and the likelihood that payment for it would be denied. GAO estimated the average retail cost of the drugs in a "typical" treatment regimen at about $4,800.

[2]These compendia, published by the U.S. Pharmacopeia, the American Hospital Formulary Service, and the American Medical Association, present evidence of a drug's effectiveness that extends beyond its labeled indication.

Effects of Reimbursement Policies

Oncologists have at least two responses to what they perceive as restrictive reimbursement policies. One is to alter the preferred treatment and the other is to change the setting in which care is provided. From 8 to 10 percent of the respondents reported altering therapies for the more difficult to treat cancers because of reimbursement problems for off-label use. (Another 15 to 28 percent reported altering therapies for these cancers because of other financial factors.) GAO did not set out in this study to evaluate quality of care; thus, the survey data do not reveal whether quality is affected either positively or negatively by reimbursement policies. Survey results show the considerable effect of reimbursement policies on the site of care. The majority of respondents (62 percent) indicated that they had admitted patients to hospitals in order to circumvent anticipated reimbursement problems in providing chemotherapy in an outpatient setting.

Recommendations to the Secretary of HHS

In summary, GAO found that the use of off-label drugs is widespread, that reimbursement denials for such use are also widespread, that reimbursement policies can influence how cancer patients are treated, that these policies can vary from one state to another, and that oncologists consider the frequently shifting policies to be confusing. This pattern of findings suggests that a clearly stated policy on when insurers should or should not pay for off-label drug use would be beneficial.

Accordingly, GAO recommends that the Secretary of Health and Human Services (HHS) issue a policy for Medicare reimbursement for off-label drug use. This policy should provide a clear basis upon which health insurers that serve as intermediaries for the Medicare program can make uniform decisions regarding reimbursement for off-label drug use.

Whatever that eventual policy may be, the rapid changes taking place both in the treatment of cancer patients and the financing of care make it imperative that the policy be periodically reviewed to ensure that it remains beneficial. Therefore, GAO also recommends that the Secretary of HHS arrange for an evaluation of the policy within 2 years of its enactment.

Agency Comments

GAO did not obtain written agency comments. However, GAO presented separate briefings on the findings of this study to officials from the relevant offices within HHS. Points raised in these briefings have been incorporated into the text of this report where appropriate.

Contents

Figures

Abbreviations

AIDS	Acquired immunodeficiency syndrome
FDA	Food and Drug Administration
GAO	General Accounting Office
HCFA	Health Care Financing Administration
HHS	Department of Health and Human Services

Introduction

Chemotherapy and Off-Label Drug Use

Chemotherapy is the use of drugs to treat cancer, a general term for a number of diseases that involve the uncontrolled growth and spread of abnormal cells. Used alone, or in combination with surgery or radiotherapy, chemotherapy is a growing part of the armamentaria available to oncologists (physicians who specialize in treating cancer) to combat the more than one million new cases of cancer estimated for 1990.[1] Anticancer drugs, usually given in combinations, can cure some patients or relieve the symptoms of those with terminal cancer.

The benefits of chemotherapy must be weighed against the reality that the drugs both are toxic and have limited effectiveness against many types of cancer. Recently, health insurers (third-party payers) have begun to deny payment for forms of chemotherapy they believe are of unproven benefit. Oncologists have expressed concern that the growing number of denials for reimbursement pose a threat to the quality of care afforded cancer patients in this country.

The specific concern of oncologists is that payers are denying reimbursement for a practice referred to as "off-label drug use" (that is, using drugs approved for one type of cancer to treat other types). This study examines reimbursement denials for off-label use. In this chapter, we present the specific objectives of the study.

Off-Label Drug Use

Amendments to the Federal Food, Drug, and Cosmetics Act in 1962 charged the Food and Drug Administration (FDA) with evaluating the effectiveness and safety of all new drugs. In its evaluation, the FDA reviews evidence provided by manufacturers that drugs will have the effect they are represented to have. Once the FDA concludes that this evidence is sufficient to demonstrate safety and effectiveness, the drug is approved for marketing. As part of that approval, information about the drug is provided in a "label" or "package insert." Included in this information is an indication of the medical conditions (hypertension, gastritis, and so on) against which the drug has been demonstrated to be effective. The label identifies only those uses for which the manufacturer has conducted studies and has demonstrated, to FDA's satisfaction, substantial evidence of safety and effectiveness.

Once FDA approves a drug, physicians can use it in any way they see as medically appropriate. This means that they can prescribe a drug for

[1] American Cancer Society, "Cancer Statistics 1990," Cancer Journal for Clinicians, 40:1, Jan./Feb. 1990.

any medical condition, irrespective of whether that condition is included on the label for the drug.

One form of off-label use in the cancer field is when research is conducted into the effectiveness of drugs for treating types of cancer other than those for which they have been labeled. (For example, when a drug labeled effective against breast cancer is given to colon cancer patients in a clinical trial). In those cases where such research bears fruit and the drugs do prove effective for different forms of cancer, the results are published and can lead to another type of off-label use: oncologists prescribing a drug that is of proven benefit. In fact, it is even possible that for a specific form of cancer, a drug given off-label may have been proven to be more beneficial than any drug labeled for that cancer.[2]

The category "off-label use" runs from clearly experimental use to standard therapy and even to state-of-the-art treatment. This variation presents problems for those attempting to formulate policies on reimbursement for off-label drug use.

The Policy Context for Off-Label Use

The FDA formally stated in its April 1982 Drug Bulletin that off-label drug use may be appropriate and rational in certain circumstances and may, in fact, reflect approaches to drug therapy that have been extensively reported in the medical literature. More recently, during 1989 hearings before the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS (acquired immunodeficiency syndrome), an FDA official said that it is not the agency's policy, intent, or bias to indicate that off-label uses are wrong, improper, or even investigational.

The U.S. Congress, in describing drug use that is appropriate, medically necessary, and not likely to have adverse medical results did not mention the labeled indication as a criterion.[3] Rather, the two standards used were the peer-reviewed medical literature and three drug compendia. These compendia, published by the United States Pharmacopeia,

[2]When studies show a drug is effective for conditions other than those included on the label, the manufacturer can ask the FDA to make a formal change in the label that would reflect the expanded benefits of the drug. However, representatives from the pharmaceutical industry characterize this process as cumbersome, time-consuming, and expensive compared to the payoff for a company. In addition, generic drug manufacturers can typically market the same drug at a reduced price after the patent expires; thus, the drug developer has little incentive to expend resources on testing the effectiveness of a drug against off-label indications.

[3]P.L. 101-508, Omnibus Reconciliation Act of 1990.

the American Hospital Formulary Service, and the American Medical Association, present evidence of a drug's effectiveness that extend beyond its labeled indications. (Appendix II describes the uses of the drug Mutamycin (mitomycin) as contained on a package insert and in one of the drug compendia.)

Health insurers have argued that a drug given off-label constitutes "investigational" therapy. This characterization is apparently based on the fact that no official determination has been made that the drug benefits the specific medical condition for which it is being provided. Further, third-party payers argue that because the therapy is investigational, its costs should not be reimbursed under the terms of their contracts, which explicitly state that they do not pay for experimental therapies.

The position of some third-party payers that off-label use is not reimbursable may be changing because of policy guidance from various sectors. For example, in a January 1989 Federal Register, the Health Care Financing Administration (HCFA), which administers the Medicare program, announced a proposed policy on off-label drug use. It sought to clarify its position by establishing the circumstances under which specific health care technologies could be considered "reasonable" and "necessary" and, therefore, reimbursable treatments. Past problems interpreting these terms led HCFA to propose defining them to mean that the procedures will be considered safe and effective as long as they are not experimental. With respect to off-label use, HCFA stated that drugs may be considered safe and effective when used for indications other than those specified on their labeling as long as the FDA has not specified otherwise, and when the use is based on authoritative evidence, or the service is generally accepted in the medical community as safe and effective for the conditions for which it is used.

The proposed rule did not, however, specifically mention the three drug compendia as sources of authoritative evidence or take away contractor discretion over coverage of off-label uses based on their own assessment of reasonable and necessary care.[4] Further, HCFA has made it clear that variations in contractors' policies on coverage are appropriate and even

[4]There are 57 intermediaries and 48 carriers responsible for administering Medicare Parts A and B, respectively. Under Medicare Part A, intermediaries reimburse providers, such as hospitals, for patient services under a prospective payment system. Under Medicare Part B, carriers reimburse physicians for reasonable charges.

desirable in certain situations and that the term "reasonable" encompasses cost-effectiveness considerations in making Medicare coverage determinations.

In addition to the efforts HCFA has made to clarify its guidance to Medicare contractors, two major insurance trade associations have recently reversed prior recommendations to their members regarding coverage of off-label uses and have specifically referred to the drug compendia as authoritative sources for determining coverage policy. In an October 1989 hearing before the National Committee to Review Current Procedures for Approval of New Drugs for Cancer and AIDS, both the Blue Cross and Blue Shield Association and the Health Insurance Association of America stated that off-label drug use should no longer be considered ineligible for coverage on the basis of being investigational treatments.[5] However, association representatives emphasized that their recommendations are only advisory, as they do not set coverage policies.

Past Studies of This Issue

The extent of off-label drug use, payers' policies regarding reimbursement for that use, and the consequences of those policies have been the subjects of a number of recent studies. In 1987, a University of Washington Family Medicare Center study found that of 500 drugs evaluated, 46 were used for off-label indications. In this study, as in a later one, investigators also found that physicians were often unaware of the labeled indications of various drugs.

The Association of Community Cancer Centers has supported several surveys of the issue and has publicized the problems that oncologists have had in obtaining reimbursement for some off-label drug use.[6] For example, in 1986, the Association audited 3,500 medical records and found that physicians were commonly prescribing drugs off-label and that the financial implications of such practices were significant.[7] In addition, through limited surveys conducted in 1987 and 1989, the Association found that 65 percent of all anticancer drug use was off-label

[5]These two trade associations represent the 74 independent Blue Cross and Blue Shield Plans and some 320 insurance companies (85 percent of commercial health insurance), respectively. They do not, however, represent the growing number of companies who opt for self-insurance.

[6]The Association represents 400 member institutions (about 5 percent of U.S. hospitals) that manage about 25 percent of all cancer patients.

[7]For the eight leading drugs reviewed, the study found that off-label uses represented almost half of the total annual sales of the drugs.

and that 67 percent of those responding said that third-party payers had denied reimbursement because the use was off-label.

Objectives, Scope, and Methodology

Previous studies of off-label drug use have been limited by their inability to present detailed information that was applicable both to the nation as a whole and to specific states. In addition, before this study, the extent of off-label use by patient type and disease was unknown as were the consequences of reimbursement denials for off-label use. Our study, requested by the Senate Committee on Labor and Human Resources, was structured to fill these gaps in knowledge.

Objectives

The Committee asked us to answer three evaluation questions pertaining to off-label anticancer drug use. They are:

- To what extent are approved anticancer drugs prescribed for off-label uses, and how does this vary by patient characteristics, therapeutic intent, and type of cancer?
- To what extent are third-party payers reimbursing physicians for the cost of anticancer drugs when they are prescribed for off-label uses?
- To what extent have physicians altered the way they treat cancer patients because of difficulties in obtaining adequate reimbursement for off-label drug use?

Scope and Methodology

Three factors defined the scope of our work: the study was limited to an examination of off-label use for cancer patients; the data collection was conducted during the spring of 1990; and the data were collected only from physicians who were members of the American Society of Clinical Oncology—the professional association that represents, among other oncologists, those physicians formally trained to provide chemotherapy. The implications of these factors are discussed in the study strengths and limitations section below.

The primary data collection mechanism for this study was a questionnaire, developed with the assistance of independent medical oncologists, professional associations, and staff from the National Cancer Institute. During January 1990, we pretested the questionnaire with seven medical oncologists practicing in Arizona, Colorado, Indiana, and Michigan. We selected oncologists from different regions of the country because during our initial examination of the issue, we learned that reimbursement policies varied considerably across states.

There were three sections to the questionnaire. The first asked respondents to provide information on the next three patients they met with after receiving the questionnaire. In this section, we asked for information on the patient (age, gender), the disease (stage, histology), and the treatment (specific drugs, other modalities of therapy).

The second part of the questionnaire asked respondents to indicate the drugs they used to treat 11 specific forms of cancer. These cancers (listed in the next chapter) were selected with the help of the National Cancer Institute to reflect both diseases for which there were standard regimens of chemotherapy and diseases for which there was no agreement on a standard medical approach.

The final section of the questionnaire was structured to explore the experiences of the respondents with reimbursement policies. This section addressed both general issues (for example, to what extent is it difficult to keep up with the reimbursement policies of third-party payers) and specific issues (what actual drugs for what types of cancer resulted in reimbursement denials).

We developed a sampling scheme that would allow us to produce generalizable estimates both for the nation and for the 11 states with the greatest number of cancer cases.[8] A sample of 1,470 oncologists was taken from the 1990 Society's membership roll. Data collection ran from March 3 to June 1, 1990, and included follow-up letters and direct phones calls to encourage survey recipients to respond. We received 681 completed questionnaires, which included data on 2,018 cancer patients. The final response rate for our survey was 56 percent, as 259 of our original sample size were not valid respondents (that is, they were retired or were researchers who do not treat patients). Appendix I presents the confidence intervals for each of the more important variables discussed in our report and also includes an analysis comparing respondents to nonrespondents. This analysis demonstrates that there is no reason to assume bias in our sample.

In a briefing report to the Chairman, Senate Committee on Labor and Human Resources, Off-Label Drugs: Initial Results of a National Survey (GAO/PEMD-91-12BR, Feb. 25, 1991), we provided the statistical results of each question on our survey.

[8]The sample was drawn with a desired precision level of 7 percent. The states included are California, Florida, Illinois, Massachusetts, Michigan, New Jersey, New York, North Carolina, Pennsylvania, Ohio, and Texas.

Study Strengths and Limitations

The major strengths of our study are its specificity and its generalizability. With respect to the former, our findings present detailed, clinically-relevant information (primary site and stage) along with the specific treatment regimen. This specificity is beneficial in demonstrating the exact circumstances under which off-label drug use is occurring.[9] The generalizability is essential because it allows us to be confident that our findings are significant, in both a statistical and a policy sense.

Our study has three limitations. One is that because reimbursement decisions can take many months to be finalized, we were unable to obtain data on decisions made for the specific patients described by the respondents in the first part of our questionnaire. As an alternative, we asked for more general types of information on reimbursement policies. Thus, we cannot report on such precise issues as the percentage of times reimbursement was denied for a specific drug.

The second limitation of our study is that it presents data for one time (spring 1990) for an issue that is in a state of flux. How cancers should be treated and what health insurers should pay for are questions that are unlikely to be answered the same way from one month to the next. Our findings, therefore, must be considered recognizing that both the number of drugs and the costs of those drugs are likely to increase greatly in the near future. For example, a 1989 survey of major drug companies found that an additional 92 anticancer drugs, then in clinical trials or being reviewed by the FDA, may be added to the 50 or so drugs and hormonal agents being marketed to treat cancer patients at the time we conducted our study.[10] In addition, it is likely that an increasing percentage of these drugs will be "biologics"; that is, genetically engineered entities, which can be very expensive.[11]

Finally, because we did not set out to evaluate quality of care in this study, the data collected from the survey do not allow the determination

[9]Rather than ask oncologists to report the extent of their off-label drug use, we determined whether or not their use of a drug was prescribed according to its label by referring to the Physicians' Desk Reference—a source that documents drug labels.

[10]Pharmaceutical Manufacturers Association, New Medicines for Older Americans (Washington, D.C., 1989).

[11]Of the 92 anticancer drugs being developed, 27 represent an expanding number of biotechnology-based products (up from 19 in 1988). Most of these newer drugs, particularly the biologics, are costly to develop and produce. Examples of these biologics include interferon, interleukin, and colony stimulating factors.

of whether quality is affected either positively or negatively by physician prescribing patterns or insurer reimbursement actions.

Our work was performed in accordance with generally accepted government auditing standards. Relevant agencies within the Department of Health and Human Services (HHS) were briefed on the results of this study, and their comments were incorporated where appropriate.

Report Overview

This report answers each of the evaluation questions in turn. Chapter 2 uses data from the patient-based portion of the questionnaire to report on the prevalence of off-label drug use. Chapter 3 addresses the extent of reimbursement problems pertaining to off-label drug use reported by responding oncologists. Chapter 4 discusses the effect reimbursement policies are having on the treatment of cancer patients. Finally, chapter 5 presents the implications of our findings and includes recommendations to the Secretary of HHS to set a policy on HCFA's coverage of off-label drug use.

Patterns of Off-Label Drug Use

Background

To answer our first study question—the extent of off-label drug use in the treatment of cancer and how that use varied—we asked a nationally representative sample of oncologists to provide information on patients for whom they prescribed an anticancer drug therapy. Our survey produced data on 2,018 patients, of whom slightly more than half (55 percent) were female. The most prevalent forms of cancer represented by these patients were breast (21 percent), colorectal (14 percent), and lung (about 13 percent). Table 2.1 shows the percentages of patients within our sample being treated for 15 prevalent forms of cancer.

Table 2.1: Patients With Prevalent Forms of Cancer

Cancer type[a]	Percent[b]
Lung	12.6
Colorectal	14.0
Breast	21.0
Prostate	2.6
Bladder	2.1
Uterus	1.2
Non-Hodgkin's lymphoma	6.9
Head and neck	2.2
Pancreas	1.4
Leukemia	6.2
Skin	1.4
Kidney	2.2
Stomach	1.7
Ovary	6.9
Brain and nervous system	2.5

[a]The cancer types are ranked by their estimated occurrence for 1990 among new patients in the United States: from 157,000 cases of lung cancer to 15,600 cases of cancer of the brain and nervous system.

[b]Since the questionnaire was sent primarily to medical oncologists (who treat cancer with drugs), the sample overrepresents those cancers that are frequently treated with chemotherapy (such as the lymphomas, leukemias, breast and ovarian cancers) and underrepresents those diseases where chemotherapy is not as frequently used as first-line treatment (such as prostate, bladder, and uterine cancers).

Our respondents reported that they were treating the majority of the patients in our sample (56 percent) with palliative intent (to relieve the symptoms of their cancers); the other 44 percent of the patients received treatment intended to cure their diseases. Three out of every four patients had already received treatments with other modalities of therapy, including chemotherapy. Surgery was the most prevalent

among these (46 percent of all patients), with radiation therapy (22 percent) and hormonal therapy (9 percent) also represented. Approximately one-third of the patients (32 percent) had previously been treated with some form of chemotherapy.

The questionnaire listed 50 anticancer drugs and hormonal agents from which respondents could identify the drugs they prescribed in treating each of three cancer patients.[1] Four of the fifty drugs on our list were not prescribed to any patients. The other 46 were prescribed to at least one patient and some patients received investigational drugs as part of a research protocol. The most frequently prescribed drugs were: fluorouracil, cyclophosphamide, doxorubicin, cisplatin, vincristine, etoposide, methotrexate, and prednisone. Table 2.2 shows the number of times these drugs were used and the percent of all drug administrations accounted for by that use. As will be shown later (in figure 2.3), the three most prescribed drugs are primarily used in treating on-label indications.

Table 2.2: Frequently Used Drugs and Their Percent of Total Use[a]

Drug	Times used	Percent
Fluorouracil	673	12.8
Cyclophosphamide	671	12.8
Doxorubicin	495	9.4
Cisplatin	430	8.2
Vincristine	342	6.5
Etoposide	326	6.2
Methotrexate	295	5.6
Prednisone	268	5.1

[a]The 2,018 cancer patients in our sample were prescribed a total of 5,239 drug administrations.

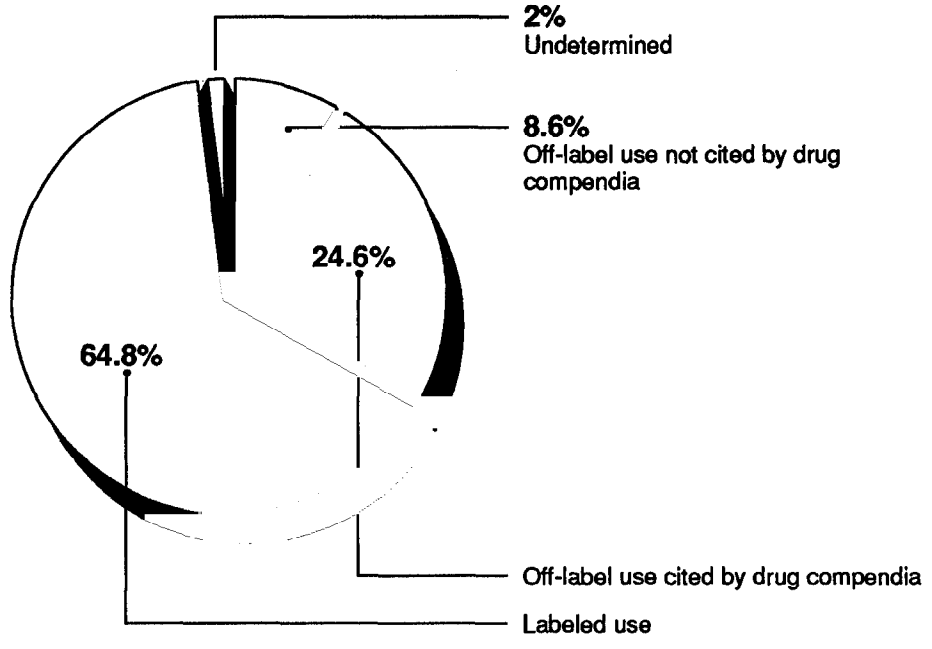
Extent of Off-Label Drug Use

By comparing the drugs prescribed by respondents to the cancers being combatted, we determined that about 33 percent of all drugs administered were used off-label. The majority (74 percent) of these off-label uses were consistent with information contained in at least one of the three major drug compendia. Approximately one-quarter (26 percent) of

[1]The drug list was developed with the assistance of oncologists and staff of the National Cancer Institute. It was intended to contain most of the anticancer drugs and hormonal agents labeled for treating cancer. Some oncologists reported using a few other drugs labeled for cancer treatment, but their use was limited.

the total off-label use was not cited in those compendia.[2] (Figure 2.1 shows the extent of off-label use.)

Figure 2.1: Drug Administrations by Type of Use



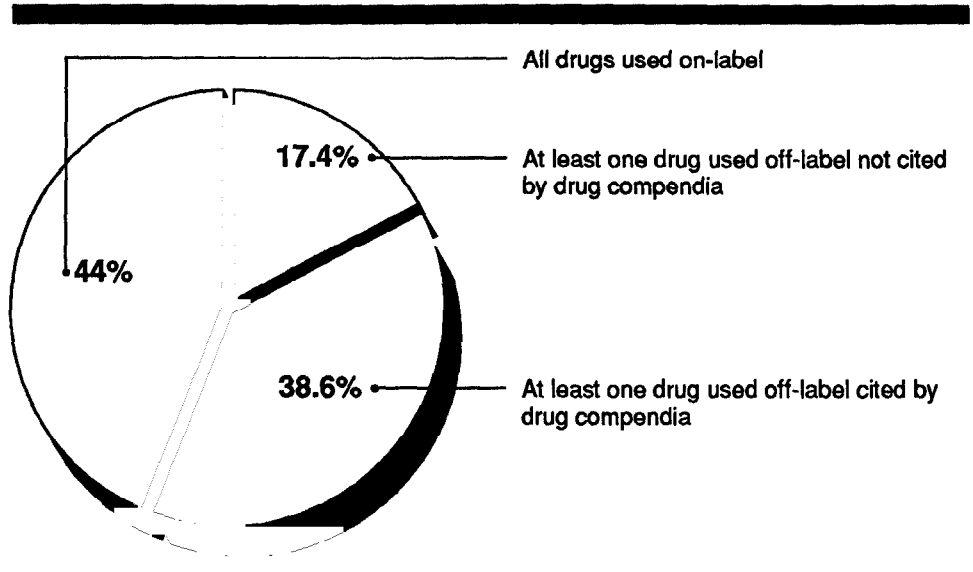
Note: The category "undetermined" represents the percent of patients who were given chemotherapy for cancers at unspecified sites in the body. We could not determine if the drug use matched its labeled indications because the site was not specified.

Of the 46 approved anticancer drugs and hormonal agents prescribed by oncologists, 44 were prescribed at least once to treat an off-label indication. Cisplatin, used primarily in the treatment of lung cancer, represented about a fifth (21.3 percent) of the total off-label use cited in the drug compendia. Prednisone, used primarily to treat breast cancer and multiple myeloma, represented a little less than a fifth (17.4 percent) of the total off-label use not cited in these sources.

[2]The terms "cited" and "not cited" are used in this report to characterize off-label use based on whether support for this use is contained in one of the drug compendia. The terms should not be viewed as reflecting the quality of care. As noted earlier, the compendia may not yet have been revised to reflect new evidence in a rapidly moving area of research. Thus, uses not cited in the drug compendia are not necessarily inappropriate uses.

Figure 2.2 shows that more than half of the patients (56 percent) were prescribed at least one drug off-label as part of their chemotherapy regimen. Again, more patients (38.6 percent) were prescribed at least one drug off-label that had cited support in the drug compendia than those patients (17.4 percent) that received at least one drug off-label that did not have cited support in these sources.[3] If more detailed histologic (type of tissue) data are included in determining the percent of patients receiving at least one drug off-label, patients receiving compendium-cited off-label uses of drugs remains about the same. However, when histology is controlled for, the percent of patients receiving at least one drug off-label for a use not cited in the drug compendia increases to about 28 percent of the total number of patients.

Figure 2.2: Percent of Patients Prescribed at Least One Drug Off-Label



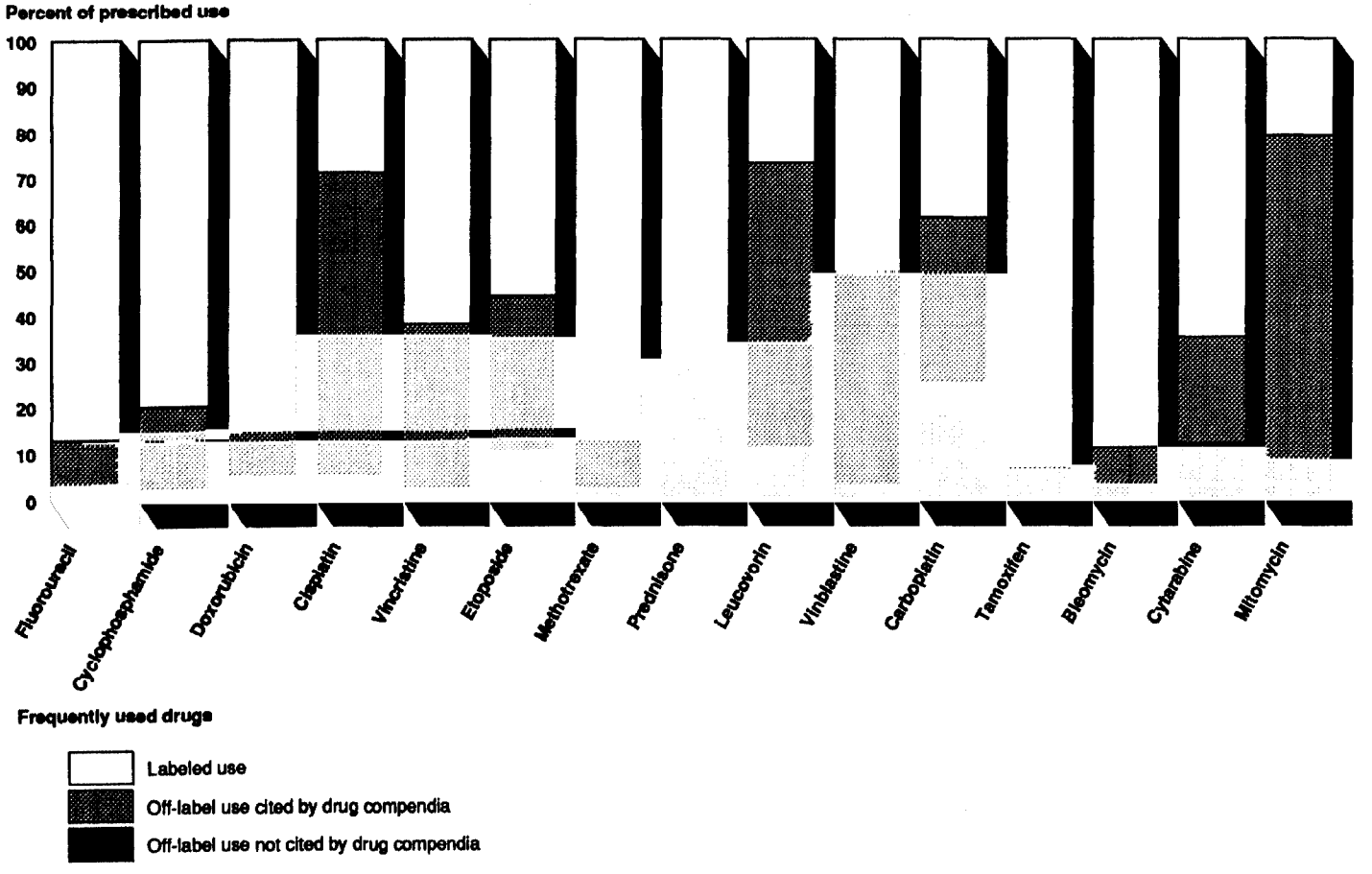
There seems to be little relationship between the frequency with which drugs are administered and the extent to which they are given off-label. Figure 2.3 shows the extent to which each of the 15 most frequently administered drugs was used off-label.[4] Except for the three most prevalently prescribed drugs, the off-label use of the remaining drugs varies

[3]These percentages reflect those patients for whom we could compare the drugs prescribed against identified cancer sites or hematologic malignancies, such as lymphomas or leukemias. For about 5 percent of the patients, we lacked enough information to make these comparisons.

[4]The number of drug administrations represents the number of times a drug was prescribed in treating the 2,018 patients in our sample. This number does not take into account the drug's dose level or the number of cycles the drug was given in a treatment regimen.

considerably. However, the next two most prevalently prescribed drugs (ifosfamide and interferon—not shown) were both used for off-label indications about 85 percent of the time.

Figure 2.3: Off-Label Use for Frequently Prescribed Drugs



Note: The drugs are ranked by the number of times they were prescribed, beginning with fluorouracil (673 times) and ending with mitomycin (85 times). Not shown are ifosfamide, interferon, and mitoxantrone, which were prescribed off-label 85 percent of the time.

Variations in Off-Label Drug Use

Patient-based data from our questionnaire show that the prescribing of drugs off-label across age group and gender was generally similar.[5] Sixty-nine percent of the male patients received at least one drug off-

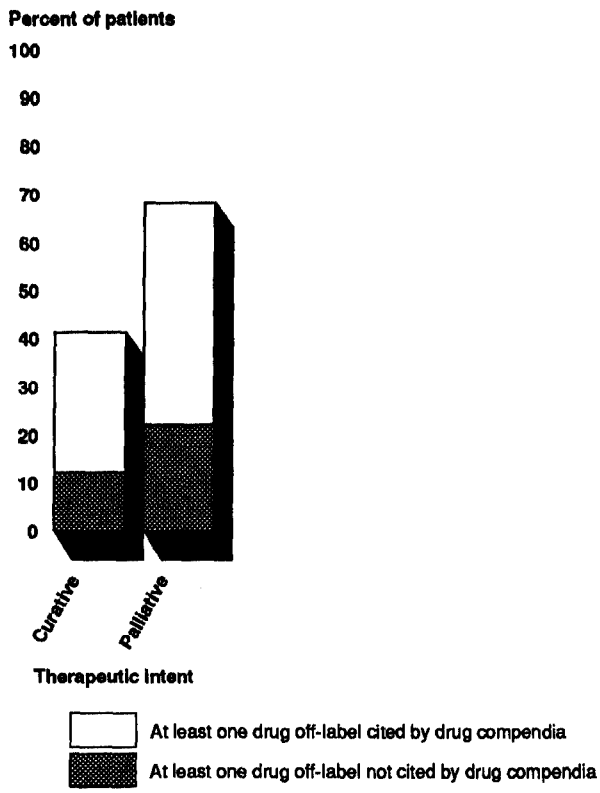
[5]We also found that those patients treated as part of a research study varied little in the extent to which they were prescribed drugs off-label from those patients who were not on a research protocol.

label in their chemotherapy regimen compared to 45 percent of the females; however, this difference is explained by the high prevalence of breast cancer in our sample, which is primarily treated with drugs used according to their label. The survey results do show some interesting variation in the extent of off-label use between palliative and curative care, across disease stages, and among types of cancer. These are discussed below.

Variation by Therapeutic Intent

Analysis showed that the extent of prescribing drugs off-label varied significantly by the intent of the therapy being given to the patient. About two of three patients receiving palliative therapy (68 percent) were treated with at least one drug off-label compared to 41 percent of the patients receiving curative care. (See figure 2.4.)

Figure 2.4: Off-Label Use by Therapeutic Intent

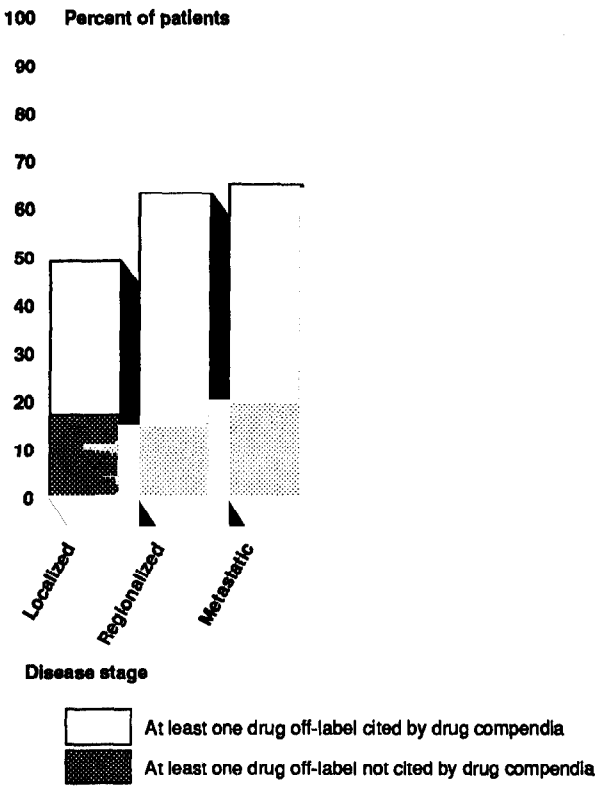


Note: While curative treatments are therapies meant to alter the course of the disease, palliative treatments are therapies that relieve symptoms, such as pain, but do not cure the patient.

Variation by Disease Stage

The prescribing of drugs off-label was also higher when the cancer being treated had metastasized to distant sites in the body. About 65 percent of the patients with metastatic cancer received at least one drug off-label as compared to about 49 percent of those with localized cancer. In cases where the cancers were localized, about 78 percent of the treatments were curative, while about 82 percent of the treatments were palliative for metastatic cancers, which are more difficult to treat and may require more lines of treatment.[6] The treatment of regionalized cancers approximates that for metastatic cancers. (See figure 2.5.)[7]

Figure 2.5: Off-Label Use by Stage of Disease



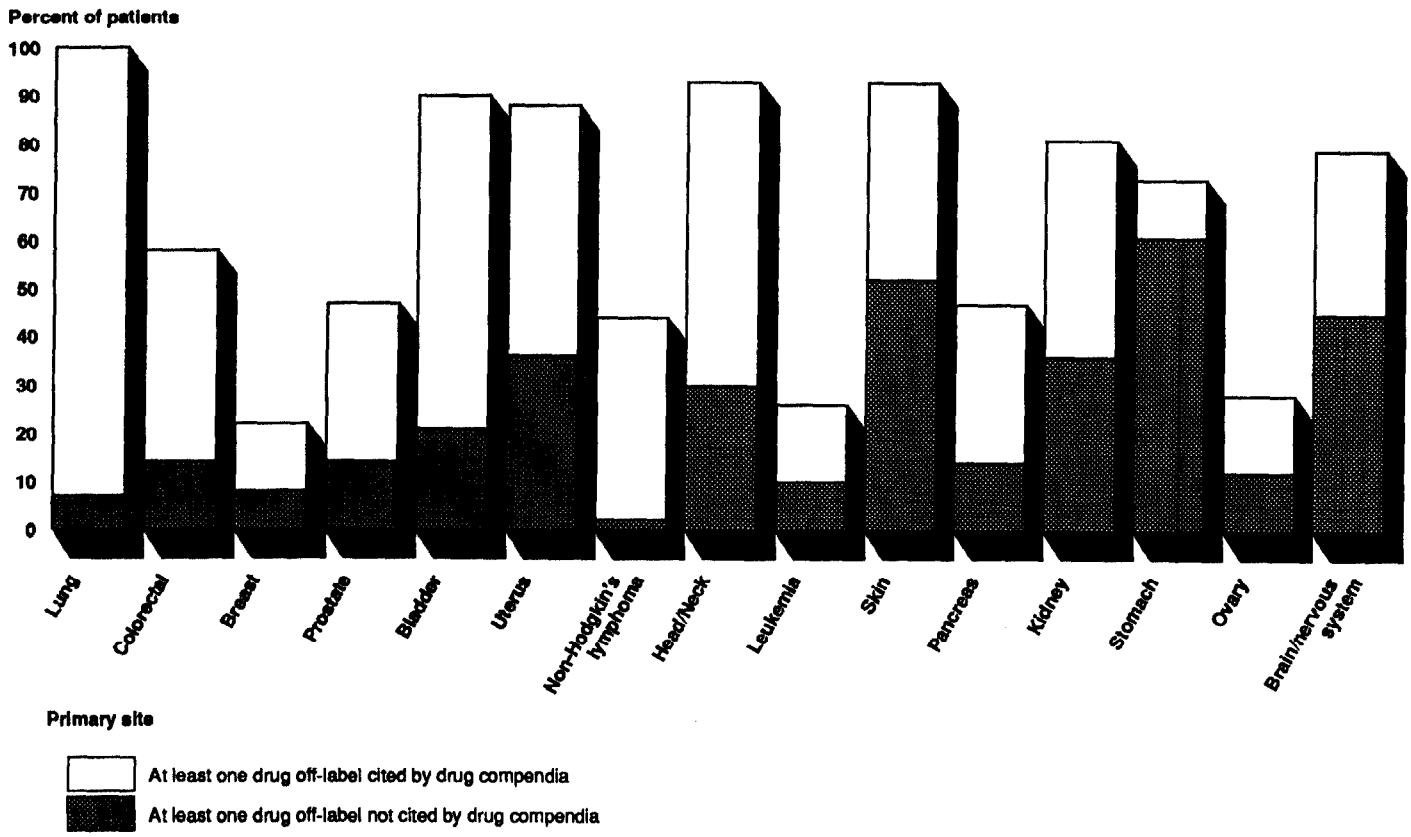
[6]For a patient who is not responsive to a particular chemotherapy regimen, an oncologist may alter the drugs used in the regimen two or three times to improve responsiveness. These alternative therapies are known as lines of treatment.

[7]A cancer that is localized is one that is still confined to its site of origin, such as the breast. A cancer that is regionalized is one that has spread from its original site to nearby surrounding areas of the same body location. A cancer that is metastatic is one that has spread to distant areas of the body by way of the lymph system or bloodstream.

Variations by Type of Cancer

Our findings show a considerable variation in how often drugs were prescribed off-label according to the type of cancer. Figure 2.6 ranks the cancers by their prevalence in society and compares, for each disease, the percent of patients that were prescribed at least one drug off-label, either cited or not by the drug compendia. The data show that there were at least some prevalent diseases (for example, lung and colorectal cancers) where more than half of the patients were treated with at least one drug off-label.[8] In some cases, such as lung cancer, almost all patients received one or more drugs off-label.

Figure 2.6:



Note: The types of cancer are ranked by their estimated occurrence for 1990 among new patients in the United States: from 157,000 cases of lung cancer to 15,600 cases of cancers of the brain and nervous system.

[8]If the use of the drug "levamisole," which was a treatment investigational new drug at the time of the survey, was included as an off-label use not cited in the drug compendia, the number of colorectal cancer patients receiving at least one drug off-label would be much higher.

Patterns Across Selected Diseases

To determine whether any systematic patterns exist in the prescribing of drugs off-label, we selected specific diseases to examine. Our criteria for selecting the cancers (with the help of staff from the National Cancer Institute) were to represent those that differ by the efficacy of their chemotherapy treatment and by the extent to which these treatments have been standardized in the medical literature. The 11 types of cancer were:

- acute nonlymphocytic leukemia,
- breast cancer in premenopausal women,
- breast cancer in postmenopausal women,
- metastatic breast cancer,
- localized (Duke's C) colon cancer,
- metastatic colon cancer,
- Hodgkin's disease (Stages IIIB, or IVA, or IVB),
- hormone refractory prostate cancer,
- small cell lung cancer,
- non-small cell lung cancer, and
- malignant melanoma.

Unlike the patient-based information in the first part of our questionnaire, we asked oncologists on the second part to report all the drugs they frequently use to treat each type of cancer. Thus, for these selected cancers, we were able to identify the number and type of drugs frequently prescribed across all patients rather than for specific patients.

The reports from oncologists on the drugs they use to treat the 11 cancers show that the extent of off-label drug use was low for diseases that had standard regimens of chemotherapy (breast cancer and Hodgkin's disease) and high for cancers where there was little agreement about the best way to treat patients (non-small cell lung cancer and hormone refractory prostate cancer).

Finally, we generally found that off-label drug use increased in the second and third lines of treatment (after the first line of chemotherapy failed in its therapeutic intent). This pattern basically held for the 4 of our 11 diseases where alternative lines of therapy are recognized: acute nonlymphocytic leukemia, metastatic breast cancer, Hodgkin's disease, and small cell lung cancer. For the first three diseases, which have more standardized regimens, on-label uses of drugs dominated first-line treatments, followed by an increasing number of off-label applications for less frequently used drugs in subsequent lines of treatment. In the third line of treatment for these diseases, the number of drugs used off-label

equaled or exceeded those used according to their label. For the treatment of small cell lung cancer that has advanced and is thus more difficult to treat, off-label drug use exceeded on-label applications in all three treatment lines.

The data for the drugs frequently used to treat the 11 types of cancer are presented in appendix III. Each figure in that appendix depicts the percent of responding oncologists who reported frequently using specific drugs in treating the disease, whether or not the drug was used according to its label, and the number of drugs that were reported as frequently used.

Summary

We found that the prescribing of drugs off-label is widespread. Almost all drugs were prescribed off-label at least once, and all types of cancer we examined were treated with some drugs that were used off-label. We also found that off-label use generally increased in treating the more difficult cases—either those cancers that had advanced to the point where they were no longer curable; those against which chemotherapy is relatively ineffective; or those in the second and third lines of treatment, when the search for a cure or a better way to palliate the disease becomes more desperate.

Patterns of Reimbursement Experiences

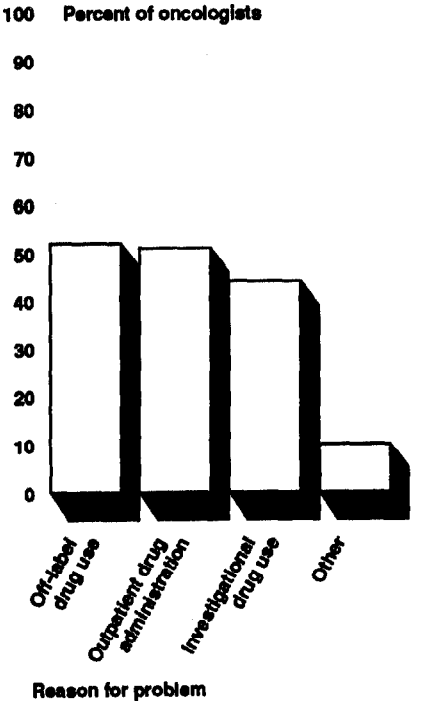
This chapter focuses on the second study question: the extent to which third-party payers are denying reimbursement for off-label drug use in the treatment of cancer patients. The chapter presents data reported by physicians on reimbursement denials for off-label drug use and then provides information on the specific treatments for which payments were reported denied. The chapter concludes by presenting the costs of the treatments, to examine whether there is any relationship between cost and the frequency of reimbursement denial.

Extent of Reimbursement Denials

Respondents reported a considerable degree of frustration with the reimbursement policies of third-party payers. Approximately two-thirds of them reported "moderate" to "very great" difficulties in staying abreast of shifts in reimbursement policy. Sixty percent claimed that there had been a moderate to very great increase during the previous 12 months in the time it took to receive reimbursement. More specifically, figure 3.1 shows the percent of oncologists reporting recent problems with reimbursement during this period in three specific categories: use of a drug in an off-label context, denials for outpatient drug administration, and use of an investigational drug.

Approximately half of the oncologists reported experiencing problems with reimbursement for off-label drug use. We wanted them to be more specific, and we asked whether they had actually been denied payment for off-label drug use. Again, we found that about half of the oncologists responded affirmatively. Another 19 percent indicated that although they had been denied payment, they had no basis to judge whether it was because of using a particular drug for an off-label indication or for another reason. Of those oncologists reporting reimbursement denials for off-label use during this time period, 76 percent indicated that the denial rate was increasing, sometimes dramatically.

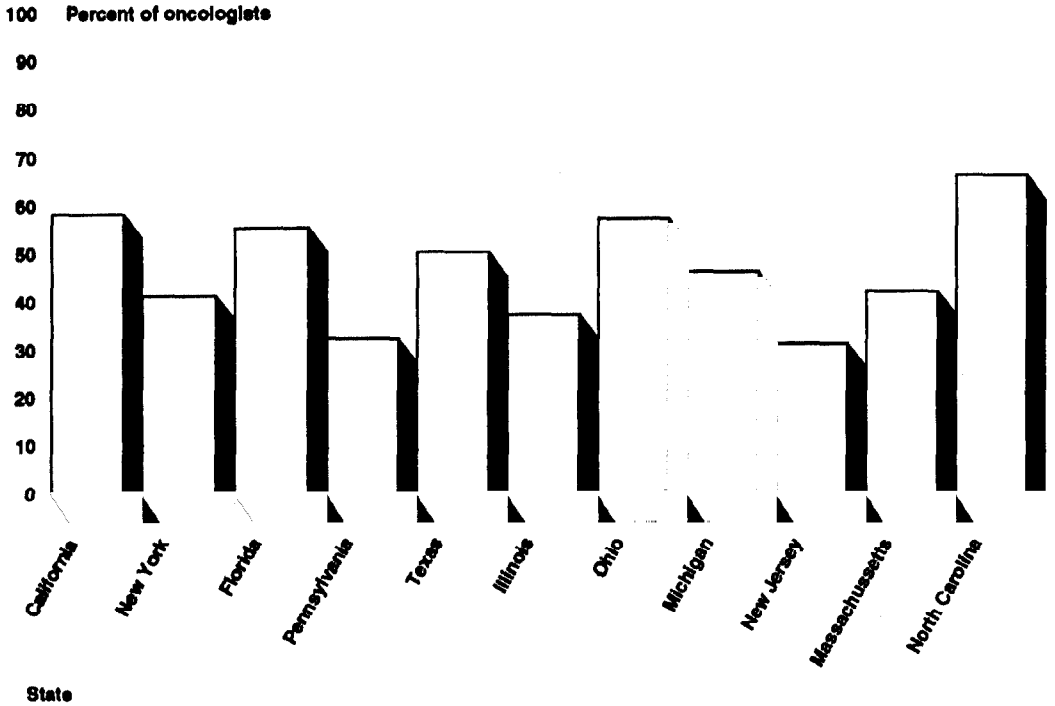
Figure 3.1: Oncologists Experiencing Third-Party Payer Problems



Note: In some cases, responding oncologists reported problems in more than one of these areas.

Our analysis indicates that reimbursement denials for off-label drug use are not limited to specific states. As figure 3.2 shows, at least 30 percent of respondents reported denials, even in those states with the lowest percentage of denials. Further, in 5 of the 11 states shown (the states with the highest incidence of cancer for which we can make statistically valid estimates), the percent of oncologists who reported payment denials for off-label drug use exceeded the percent who did not report such denials.

Figure 3.2: State-by-State Reporting of Reimbursement Denials for Off-Label Drug Use



Note: The states are ordered from left to right by the estimated prevalence of new cancer patients for all sites in 1990, beginning with California, at 105,000 new patients and ending with North Carolina, at 26,000 new patients (excluding carcinoma in situ and nonmelanoma skin cancer). Based on the response rate for each state, these data are considered generalizable to the experiences of all oncologists practicing in each state.

Aside from the prevalence of reported problems, our results also show that there is considerable geographic variation in the number of oncologists reporting reimbursement denials. This may reflect differences in the coverage policies of third-party payers across states. As evidence of this variation, 45 respondents from 19 states reported that within the previous year they had encountered situations where new patients from other states could not obtain reimbursement for treatments given, and reimbursed for, in the previous states of residence.

Although respondents reported reimbursement problems with many third-party payers, the insurer most frequently cited was Medicare. This is not surprising in light of the fact that most cancer patients are elderly and, therefore, covered by Medicare.

Drugs for Which Denials Are Frequent

Oncologists were asked to indicate the drugs for which they were unable to obtain reimbursement when they were prescribed off-label. Of the 50 drugs and hormonal agents on our drug list, only 11 had no reported instances of reimbursement denial for off-label use in the previous 12 months. In some cases, oncologists reported being denied reimbursement for a drug used off-label for more than one type of cancer.

Interferon was the drug most frequently cited as encountering reimbursement problems for its off-label use. As the first product of biotechnology on the market, this widely used drug was approved only for hairy cell leukemia and (AIDS-related) Kaposi's sarcoma at the time that our survey was conducted. Oncologists reported problems in obtaining reimbursement for the use of this drug in treating more than a dozen types of cancer.[1]

Oncologists identified 39 anticancer drugs and hormonal agents that had FDA-approved labels, but for which they reported being denied reimbursement when they used those drugs to treat off-label indications. Table 3.1 lists the drugs most frequently cited by oncologists as leading to reported reimbursement denials when used off-label. The table also presents, for each drug, the types of cancers these drugs were being used against when payment was denied. For six of the drugs, however, some of the reported off-label uses are actually authorized uses on the drug's label. This apparent discrepancy may arise for several reasons: the physician did not adequately document the medical necessity of the procedure, the mode of drug administration rather than the drug's off-label use was not covered, there was a procedural coding error, or there were erroneous responses to our question—that is, no denial actually occurred.

[1] At least one manufacturer of interferon has established a special service to help physicians obtain reimbursement from resistant third-party payers.

Table 3.1: Frequently Identified Drugs That Were Denied Reimbursement[a]

Drug	Type of cancer
Carboplatin	Lung Ovary[b]
Cisplatin	Lung
Etoposide	Breast Lung[b] Lymphoma
Fluorouracil	Colorectal[b]
Flutamide	Prostate[b]
Ifosfamide	Lung Ovary Cervix
Interferon	Bone Chronic myelogenous leukemia Colorectal Kidney Lymphoma Skin
Mitoxantrone	Breast
	Lymphoma
Leucovorin	Breast[b] Colorectal Ovary
Leuprolide	Breast Prostate[b]

[a]The off-label use of these drugs in treating some other types of cancer was also reported, but by fewer oncologists.

[b]This disease is approved for treatment on the drug's label. Etoposide is labeled for treating small cell lung cancer, but not non-small cell lung cancer.

Treatment Costs for Specific Drugs

We decided to examine the cost of using the drugs that were most often reported by oncologists as leading to reimbursement denial for their off-label use to determine if a pattern of denial based on cost existed.[2] A number of factors influence the cost of using a particular drug in a treatment regimen, such as its dose level, number of cycles given, and its mode of administration. We were able to calculate an average cost for each drug, excluding its administration costs, by approximating average

[2]Our data did not allow us to determine the number of times payment was denied for the use of a specific drug or the number of oncologists choosing not to use a drug off-label because they know the insurers in their area will not reimburse for this use.

dose levels and using a "typical" number of cycles.[3] The drugs for which we gathered cost data include three that are the most frequently administered to cancer patients: cisplatin, etopiside, and fluorouracil.

Table 3.2 provides estimates of the cost to treat a patient with drugs for which reimbursement is frequently reported as being denied. In this table, we estimated that the cost of a drug in a typical treatment regimen ranged from $36 for fluorouracil to $9,252 for ifosfamide, with a typical average cost of about $4,800. We did not see a pattern of denials based solely on cost considerations; the drugs that have been most frequently denied reimbursement for their off-label uses (i.e., interferon and carboplatin) are not the most expensive.

Table 3.2: Cost of Drugs for Which Reimbursement Is Frequently Denied

Drug	Average dose per cycle	Cost per dose		Cost per patient (6 cycles)[c]
		Wholesale[a]	Retail[b]	
Carboplatin	585.0 mg	$412/450.0 mg	$910	$5,460
Cisplatin	135.0 mg	104/50.0 mg	477	2,862
Etoposide	500.0 mg	70/100.0 mg	595	3,564
Fluorouracil	1800.0 mg	1/500.0 mg	6	36
Flutamide	22500.0 mg/mo.	2/250.0 mg	198	3,564
Ifosfamide	14.4 g	63/1.0 g	1,542	9,252
Interferon	21.0 M units	82/10.0 M units	621	3,726
Mitoxantrone	21.6 mg	365/20.0 mg	326	3,720
Leucovorin[d] (colon)	540.0 mg	24/25.0 mg	881	5,286
Leucovorin[d] (low)	27.0 mg	24/25.0 mg	44	264
Leucovorin[d] (high)	360.0 mg	24/25.0 mg	588	3,528
Leucovorin[d] (breast)	63.0 mg	24/25.0 mg	103	618
Leuprolide	7.5 mg/mo.	293/7.5 mg	498	8,964

[a]All costs are based on 1990 average wholesale prices with the exception of costs for cisplatin, interferon, and leucovorin which are 1989 prices.

[b]The retail cost per dose = (average dose per cycle) x (average wholesale price cost per dose) x (1.7). The 1.7 multiplier represents the pharmacy markup rate, except for flutamide, which is generally marked up only 10 percent.

[c]Each drug is administered an average of six times, except for flutamide and leuprolide, which are administered daily for up to 18 months.

[d]The price of leucovorin varies depending on what it is treating and whether a high or low dose level is used. It is now available at $5 per 50 mg as a generic drug.

[3]Dosages are usually given in milligrams per square meter (mg/sq m), where sq m refers to the surface area of a patient's body. An average person weighing 150 pounds and with a height of 5'8" was used to convert dosage levels to prescription levels. Such a person has approximately 1.8 sq m of surface area. Therefore, an average dose of 325 mg/sq m, multiplied by 1.8 sq m, yields a prescription level of 585 mg.

Summary

Problems obtaining reimbursement for off-label drug treatments have occurred in the past and seem to be increasing today. Approximately half (52 percent) of the oncologists who responded to our survey reported that at some time they have had reimbursement problems for the use of drugs off-label as well as for the setting where they were administered. Of these same respondents, 48 percent reported specific reimbursement denials for off-label uses of anticancer drugs in the last 12 months, and most (76 percent) thought the rate of denials was increasing.

Denials for off-label drug use were reported in all but two states surveyed and for most drugs, although there is variation. Across the 11 states for which we have representative data, the lowest percent of respondents reporting denials was 30. Of the 50 drugs or hormonal agents from our drug list that can be used in the treatment of cancer patients, 39 were identified at least once as having had reimbursement denied for their use in an off-label context. Interferon, a drug used to treat many types of cancer but only labeled for two types, was the most frequently cited as having reimbursement denied for off-label use. Finally, we found no pattern of reimbursement denial among drugs based solely on their cost.

Effects of Reimbursement Policies

A physician must consider many factors in deciding on the appropriate course of treatment for a cancer patient. The type of disease, how far it has progressed, previous treatments, and the preferences of the patient are some of these factors. In this chapter, we show that reimbursement policies also can play a role in the treatment decision. Presented below are our findings on the final question, the effect of reimbursement policies on the treatment of cancer patients. It is important to note again that our focus is on the extent to which oncologists reported altering preferred treatments and not on the effect of the therapeutic decision on the quality of care afforded cancer patients.

Altering Preferred Drug Treatments

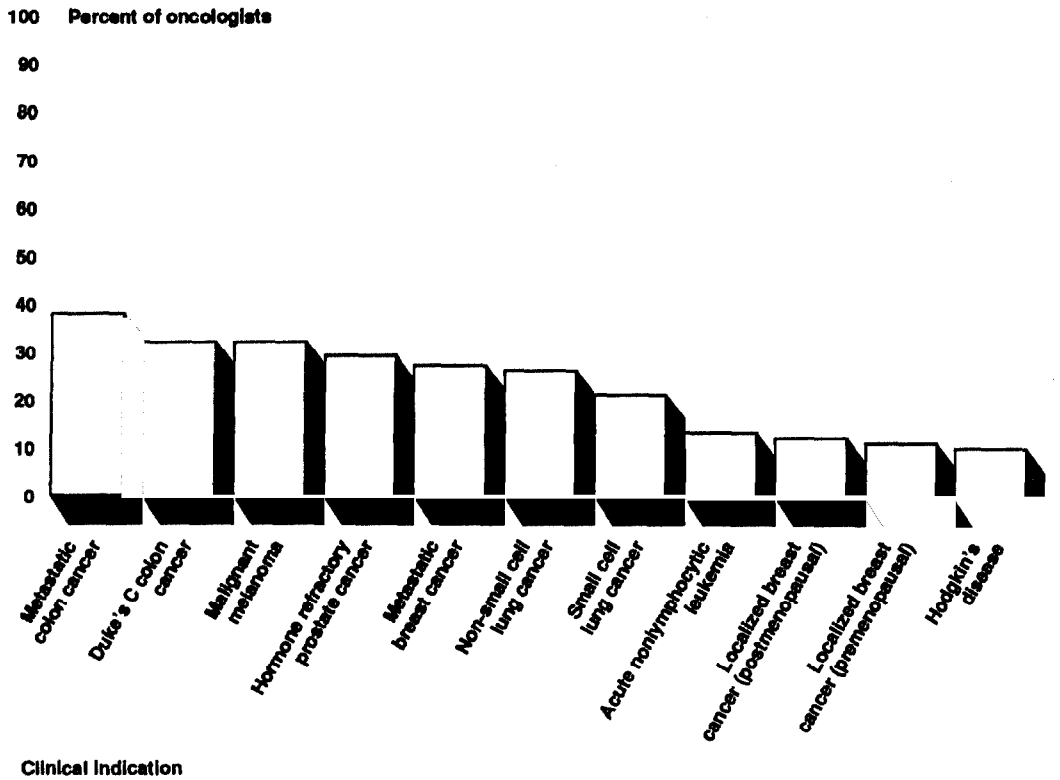
The question we posed asked the oncologists to indicate whether there was a difference between how they treat specific types of cancer and how they would like to treat these diseases. The cancers selected were the same 11 used for our examination of treatment patterns. (See appendix III.) In those situations where respondents indicated they treated patients in some way other than their preferred way of treating, we asked them to indicate which of four barriers caused them to alter their preferred treatments for each type of cancer:

- expected reimbursement denials for off-label drug use,
- denials for treatment in an outpatient setting,
- physician's concerns over the cost of the treatment,
- patient's perceived concerns about the cost.

Figure 4.1 shows the percent of oncologists that altered their preferred treatments for each of the 11 cancers. When the responses are averaged across all cancers and barriers, approximately 23 percent of the respondents claimed to have altered preferred treatments.[1] As can be seen from the figure, respondents reported altering therapies most frequently in treating colon cancer, malignant melanoma, hormone refractory prostate cancer, and even metastatic breast cancer, which is treated with fewer off-label drugs. It is important to note that colon, prostate, and breast cancer are among the most prevalent forms of cancer, and the treatment decisions made for these diseases are likely to influence large numbers of patients.

[1]Because not all oncologists treat patients in each of the 11 disease categories, the total number of oncologists responding in each case ranged from 491 who treat acute nonlymphocytic leukemia patients to 534 who treat patients with Hodgkin's disease.

Figure 4.1: Altering Preferred Treatments Because of Reimbursement and Cost Factors



Note: These percentages do not indicate how often responding oncologists altered their preferred treatments, only that they reported altering therapies for these diseases at one time because of reimbursement and drug cost factors.

Table 4.1 displays our specific findings for the reasons oncologists reported altering their preferred therapies. A little over 10 percent of respondents reported altering therapies for colon cancer and malignant melanoma because of denials of payment for off-label use. Further, between 6 and 8 percent of the respondents reported that denials for off-label use led them to alter their therapies for lung, hormone refractory prostate, and metastatic breast cancer. The table also shows that reimbursement denials for outpatient drug administrations were cited slightly more often than off-label use as a barrier to using preferred therapies.

Table 4.1: Percent of Oncologists Reporting Specific Barriers to Preferred Treatments[a]

	Payment denied for use		Cost concerns		
Cancer type	Off-label	Outpatient	Physician	Patient	Other
Acute nonlymphocytic leukemia	1.8	3.2	0.6	2.4	4.5
Localized breast cancer (premenopausal)	0.9	3.4	0.9	5.7	0.4
Localized breast cancer (postmenopausal)	1.0	2.9	1.1	7.0	0.4
Metastatic breast cancer	6.0	8.1	2.3	7.2	2.7
Localized or regional colon cancer	10.3	8.5	2.2	7.2	3.6
Metastatic colon cancer	10.4	12.9	4.9	7.4	2.1
Stage III or IV Hodgkin's disease	2.2	3.2	0.4	2.8	1.3
Hormone refractory prostate cancer	6.8	6.6	4.2	9.2	2.2
Small cell lung cancer	6.5	8.0	1.6	3.3	1.4
Non-small cell lung cancer	8.2	7.5	3.1	4.7	2.5
Malignant melanoma	10.6	9.4	2.2	6.4	3.6

[a]Because not all oncologists treat patients in each of the 11 disease categories, the total number of oncologists responding in each case ranged from 491 who treat acute nonlymphocytic leukemia patients to 523 who treat patients with Hodgkin's disease.

Circumventing Reimbursement Denials

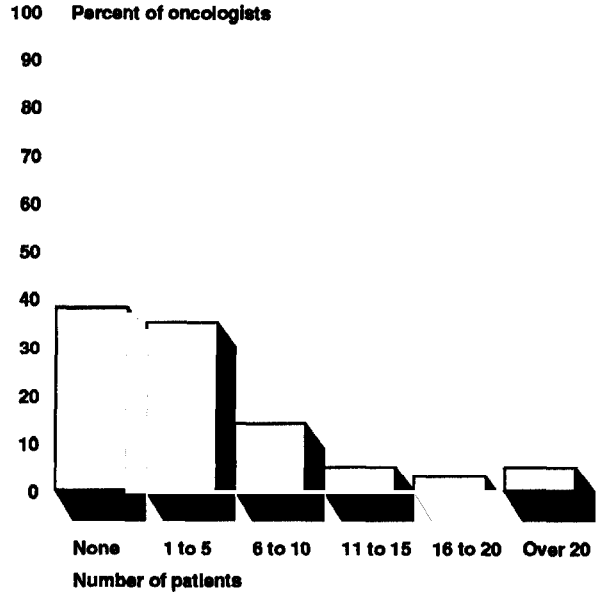
The data presented above describe situations where oncologists have responded to reimbursement denials by altering the therapy provided to their patients. Another potential response to perceived problems with reimbursement might be to try to "beat the system." During the initial phase of our study, we heard anecdotal information that oncologists may occasionally admit patients to a hospital rather than give chemotherapy in an outpatient setting so as to ensure reimbursement from third-party payers. One reason that this may occur is because of distinctions the Health Care Financing Administration (HCFA) makes between services provided in and out of the hospital.

When a patient is admitted to a hospital for treatment as part of a diagnosis-related group, reimbursement for services is automatically set by Medicare (under part A payments) through a prospective payment system. In other words, the hospital is given a fixed reimbursement fee under Medicare, irrespective of the drugs that are used in the treatment regimen. As a result, oncologists can give patients off-label drug treatments as well as investigational drugs without the scrutiny that is

applied to services rendered in their offices. In an office setting, Medicare contractors have relatively broad discretion (under part B payments) in denying reimbursement for certain drug treatments.[2]

As part of our questionnaire, we asked oncologists to report the extent to which they admit patients to hospitals solely to circumvent problems with reimbursement. As figure 4.2 shows, this is not an unusual practice. In fact, the majority of respondents (62 percent) reported that they had engaged in this practice at least once in the 3 months preceding the survey.

Figure 4.2: Ordering Hospital Admissions Because Outpatient Treatments Would Be Denied Reimbursement



Note: The number of patients admitted to hospitals for treatments that would be denied reimbursement if given as outpatients represents those admissions over a 3-month period.

We have initiated another study to examine exactly what forms of reimbursement problems are leading to what might be unnecessary hospitalization and the cost implications of this behavior. This practice might take place despite the existence of peer review organizations, which contract with HCFA to review hospital admissions and the quality of medical care provided to Medicare beneficiaries. These organizations sample

[2]Carriers, who administer Medicare part B payments are authorized by law to perform utilization reviews; that is, to determine if medical services provided to beneficiaries are medically necessary, appropriate, and promote the most efficient use of available Medicare health services and facilities.

only 3 percent of hospital admissions, and they are not required to sample cancer patients or patients with any specific disease.

Agreements With Third-Party Payers

Finally, we discovered through our survey that a small number of oncologists (44 from 18 different states) had reached formal agreements with their third-party payers to resolve reimbursement denials regarding off-label drug use. These agreements specify the conditions that must be met to obtain reimbursement for off-label drug use.

Conclusions and Recommendations

Conclusions

In the previous chapters, we have demonstrated that:

- Off-label drug use is common, and even predominant, in the treatment of cancer patients.
- Reported denial of payment for off-label use also is common throughout the country.
- Denial of payment reportedly influences the therapies provided to patients.
- The policies on reimbursement can vary from state to state.
- Finally, oncologists, who acknowledge being influenced by the reimbursement policies in selecting treatments, at the same time express frustration with their inability to keep up with reimbursement policy in general.

The sum of these facts makes it evident that an explicit policy is needed that specifies the conditions under which off-label use should, or should not, be reimbursed. The need for a policy is evident, but what that policy should be is not clear at this time. One problem is that most drug use for curable cancers is on-label while off-label use is most prevalent for the most difficult to treat cancers where there is often no curative treatment and little agreement on the best way to palliate the disease. As a consequence, health insurers, charged as they are with the responsibility to pay only for medically necessary and appropriate care, are confronted with the fact that off-label use in general can be both the most appropriate therapy from the perspective of the oncologist, yet not be very effective therapy.

Another reason for the difficulty in developing a policy for payment for off-label drug use relates to the issue of "support." Our data show that approximately 25 percent of the off-label use is not cited in any of the three major drug compendia. Reimbursement would be denied for these treatments under any policy that relied on the drug compendia for support. The problem is that although exclusion from the compendia may indicate that the drug is not beneficial (and therefore not reimbursable by insurers), it may also occur when the benefits have only recently been demonstrated. Distinguishing between these situations with a general policy remains problematic. Additionally, how a change in the role of the compendia (from reference documents to the bases for payment decisions) would change the quality, comprehensiveness, and timeliness of those documents is unclear.

Recommendations to the Secretary of HHS

Despite the problems in deciding which off-label uses should and should not be reimbursed, there is a need for an explicit policy. Absent such a policy, decisions affecting thousands of patients are being made without public scrutiny and discussion. For this reason, we recommend that the Secretary of Health and Human Services (HHS) issue a policy that states specifically the circumstances under which the Health Care Financing Administration (HCFA) will reimburse for the administration of drugs off-label in the treatment of cancer patients.

HCFA proposed such a policy to help clarify the conditions under which off-label drug use might be considered "reasonable" and "necessary" therapy and, therefore, reimbursable in January 1989. Since then, the policy has been under review at HHS. We were informed that the agency is considering the use of the drug compendia in determining what drug applications are safe, effective, and not investigational.

We believe that a policy that references the drug compendia is likely to promote more uniform reimbursement coverage of off-label drug use, as well as reduce the number of instances in which there are disputes between oncologists and third-party payers on the appropriateness of specific drug treatments. Accordingly, we recommend that the Secretary of HHS issue a final policy as soon as possible.

We also recommend that the Secretary of HHS conduct an evaluation of the policy within the first 2 years of its introduction to determine what modifications, if any, are needed. This recommendation is based on two considerations:

- It is unclear how reliance on the drug compendia for reimbursement decisions will influence the processes by which information is entered in those documents; and,
- The likely advent of new and expensive forms of therapy for cancer argues for a timely review of coverage and reimbursement policy.

Statistical Analysis

The response rate to our survey was 56 percent. A total of 1,480 questionnaires were sent out. Based on returned questionnaires and subsequent investigation, we determined that 286 of the addressees were not valid respondents because they did not treat patients with chemotherapy. Of the 1,214 valid respondents, 680 returned completed questionnaires.

In order to determine whether the nonresponse introduced any bias into our sample, we compared respondents to nonrespondents in terms of type of employment. Our assumption was that privately employed physicians might be more sensitive to reimbursement issues than their salaried colleagues. Therefore, we examined whether there were disproportionate numbers of such physicians in the group of respondents. Table I.1 presents our estimates at the 95-percent confidence level.[1]

Table I.1: Comparison of Respondents to Nonrespondents

Place of employment	Respondents	Nonrespondents
Private office	27.2 ± 2.6%	23.9 ± 2.6%
Hospital	5.8 ± 1.2	6.7 ± 1.4
Cancer center	8.6 ± 1.6	7.1 ± 1.6
Institute	1.5 ± 0.8	1.8 ± 0.9
University	8.9 ± 1.6	8.9 ± 1.7

As table I.1 shows, there was overlap in the interval estimate (the range between the lower and upper estimates) for each category. Therefore, we conclude that there were no statistically significant differences between respondents and nonrespondents in terms of place of employment.

Presented below are the 95-percent confidence intervals for the key variables in the report. The estimates are provided for the sample as a whole. Estimates at the state level, as well as the standard errors for all variables are available upon request from our office.

[1]North Carolina, the 11th state for which generalizations are made in the report, was omitted from this analysis because there were too few nonrespondents from that state.

Table I.2: 95-Percent Confidence Intervals for Key Variables

Variable	Estimate	Upper bound	Lower bound
Percent of all drugs used off-label	33.2%	37.4%	29.0%
Off-label drugs among			
All patients	55.5	60.2	50.8
Those treated for palliation	66.3	72.2	59.4
Those treated for cure	42.1	48.3	37.9
Percent of physicians hospitalizing patients to circumvent reimbursement problems	61.7	66.5	56.8

Approved Label and Off-Label Support

This appendix contains information about the drug mitomycin. Figure II.1 is a copy of the label approved by the FDA that accompanies the drug in its package. Figure II.2 contains a copy of the information about this drug taken from the American Medical Association's Drug Evaluations Annual 1991. This publication is one of the three major drug compendia that discuss the acceptable off-label uses of drugs. (The American Hospital Formulary Service and the U.S. Pharmacopeia publish the other two compendia.) The content of the actual discussion of each drug differs somewhat among the compendia.

Figure II.1: Sample Approved Package Insert Label

BRISTOL LABORATORIES
ONCOLOGY PRODUCTS

Mutamycin®
MITOMYCIN FOR INJECTION

WARNING

Mutamycin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of Mutamycin (see "WARNINGS" and "ADVERSE REACTIONS" sections).

Hemolytic Uremic Syndrome (HUS) a serious complication of chemotherapy, consisting primarily of microangiopathic hemolytic anemia, thrombocytopenia, and irreversible renal failure has been reported in patients receiving systemic Mutamycin. The syndrome may occur at any time during systemic therapy with Mutamycin as a single agent or in combination with other cytotoxic drugs, however, most cases occur at doses ≥ 60 mg of Mutamycin. Blood product transfusion may exacerbate the symptoms associated with this syndrome.

The incidence of the syndrome has not been defined.

DESCRIPTION

Mutamycin (also known as mitomycin and/or mitomycin-C) is an antibiotic isolated from the broth of **Streptomyces caespitosus** which has been shown to have antitumor activity. The compound is heat stable, has a high melting point, and is freely soluble in organic solvents.

ACTION

Mutamycin selectively inhibits the synthesis of deoxyribonucleic acid (DNA). The guanine and cytosine content correlates with the degree of Mutamycin-induced cross-linking. At high concentrations of the drug, cellular RNA and protein synthesis are also suppressed.

In humans, Mutamycin is rapidly cleared from the serum after intravenous administration. Time required to reduce the serum concentration by 50% after a 30 mg bolus injection is 17 minutes. After injection of 30 mg, 20 mg, or 10 mg I.V., the maximal serum concentrations were 2.4 μg/mL, 1.7 μg/mL, and 0.52 μg/mL, respectively. Clearance is effected primarily by metabolism in the liver, but metabolism occurs in other tissues as well. The rate of clearance is inversely proportional to the maximal serum concentration because, it is thought, of saturation of the degradative pathways.

Approximately 10% of a dose of Mutamycin is excreted unchanged in the urine. Since metabolic pathways are saturated at relatively low doses, the percent of a dose excreted in urine increases with increasing dose. In children, excretion of intravenously administered Mutamycin is similar.

Animal Toxicology — Mutamycin has been found to be carcinogenic in rats and mice. At doses approximating the recommended clinical dose in man, it produces a greater than 100 percent increase in tumor incidence in male Sprague-Dawley rats, and a greater than 50 percent increase in tumor incidence in female Swiss mice.

INDICATIONS

Mutamycin is not recommended as single-agent, primary therapy. It has been shown to be useful in the therapy of disseminated adenocarcinoma of the stomach or pancreas in proven combinations with other approved chemotherapeutic agents and as palliative treatment when other modalities have failed. Mutamycin is not recommended to replace appropriate surgery and/or radiotherapy.

CONTRAINDICATIONS

Mutamycin is contraindicated in patients who have demonstrated a hypersensitive or idiosyncratic reaction to it in the past.

Mutamycin is contraindicated in patients with thrombocytopenia, coagulation disorder, or an increase in bleeding tendency due to other causes.

WARNINGS

Patients being treated with Mutamycin must be observed carefully and frequently during and after therapy.

The use of Mutamycin results in a high incidence of bone marrow suppression, particularly thrombocytopenia and leukopenia. Therefore, the following studies should be obtained repeatedly during therapy and for at least eight weeks following therapy: platelet count, white blood cell count, differential, and hemoglobin. The occurrence of a platelet count below 100,000/mm³ or a WBC below 4,000/mm³ or a progressive decline in either is an indication to withhold further therapy until blood counts have recovered above these levels.

Patients should be advised of the potential toxicity of this drug, particularly bone marrow suppression. Deaths have been reported due to septicemia as a result of leukopenia due to the drug.

Patients receiving Mutamycin should be observed for evidence of renal toxicity. Mutamycin should not be given to patients with a serum creatinine greater than 1.7 mg percent.

Usage in Pregnancy — Safe use of Mutamycin in pregnant women has not been established. Teratological changes have been noted in animal studies. The effect of Mutamycin on fertility is unknown.

PRECAUTIONS

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids in patients who had previously or simultaneously received Mutamycin. The onset of this acute respiratory distress occurred within minutes to hours after the vinca alkaloid injection. The total number of doses for each drug has varied considerably. Bronchodilators, steroids and/or oxygen have produced symptomatic relief.

A few cases of adult respiratory distress syndrome have been reported in patients receiving Mutamycin in combination with other chemotherapy and maintained at FIO_2 concentrations greater than 50% perioperatively. Therefore, caution should be exercised using only enough oxygen to provide adequate arterial saturation since oxygen itself is toxic to the lungs. Careful attention should be paid to fluid balance and overhydration should be avoided.

ADVERSE REACTIONS

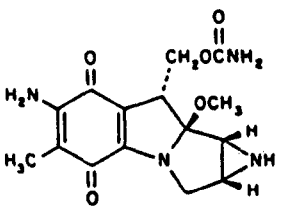
Bone Marrow Toxicity — This was the most common and most serious toxicity, occurring in 605 of 937 patients (64.4%). Thrombocytopenia and/or leukopenia may occur anytime within 8 weeks after onset of therapy with an average time of 4 weeks. Recovery after cessation of therapy was within 10 weeks. About 25% of the leukopenic or thrombocytopenic episodes did not recover. Mutamycin produces cumulative myelosuppression.

Integument and Mucus Membrane Toxicity — This has occurred in approximately 4% of patients treated with Mutamycin. Cellulitis at the injection site has been reported and is occasionally severe. Stomatitis and alopecia also occur frequently. Rashes are rarely reported. The most important dermatological problem with this drug, however, is the necrosis and consequent sloughing of tissue which results if the drug is extravasated during injection. Extravasation may occur with or without an accompanying stinging or burning sensation and even if there is adequate blood return when the injection needle is aspirated. There have been reports of delayed erythema and/or ulceration occurring either at or distant from the injection site, weeks to months after Mutamycin, even when no obvious evidence of extravasation was observed during administration. Skin grafting has been required in some of the cases.

Renal Toxicity — 2% of 1,281 patients demonstrated a statistically significant rise in creatinine. There appeared to be no correlation between

Figure II.2: Compendium-Cited Uses for Sample Drug

MITOMYCIN
[Mutamycin]



ACTIONS. Mitomycin is isolated from *Streptomyces caespitosus*. After activation by intracellular reductases, the drug functions as a bifunctional alkylating agent. Increased rates of reductive activation in hypoxic, relative to well-oxygenated, cells confer some preferential activity for mitomycin against hypoxic solid tumor cells (Sartorelli, 1988). Cytotoxicity is probably due to the inhibition of DNA synthesis that results from cross-linking of DNA. At high concentrations, RNA and protein synthesis also are inhibited. Mitomycin also can participate in free radical reactions. It is cell cycle nonspecific but appears to be most active in the late G_1 and early S phases.

USES. Mitomycin is used in the palliative treatment of various solid tumors. It is part of the FAM regimen used in gastric carcinoma (see Table 2). Other indications are non-small cell lung, cervical, colorectal, breast, bladder, pancreatic, and esophageal carcinomas.

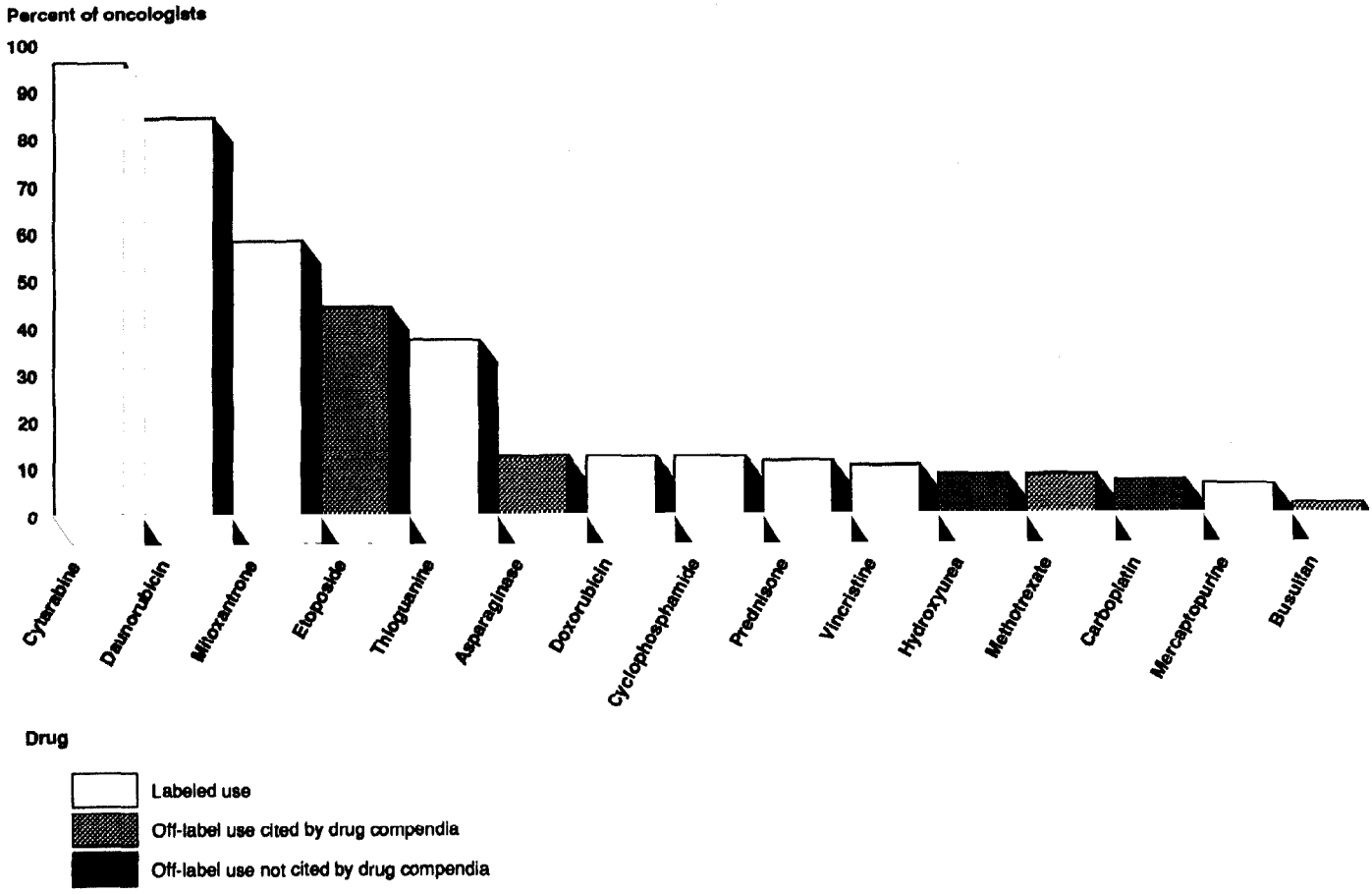
Off-Label Drug Use for Specific Indications

Figures III.1 through III.11 graphically show the drugs that most oncologists reported as using frequently to treat each of 11 specific cancers. They are:

- acute nonlymphocytic leukemia,
- breast cancer in premenopausal women,
- breast cancer in postmenopausal women,
- metastatic breast cancer,
- localized (Duke's C) colon cancer,
- metastatic colon cancer,
- Hodgkin's disease (Stages IIIB, IVA, IVB),
- hormone refractory prostate cancer,
- small cell lung cancer,
- non-small cell lung cancer, and
- malignant melanoma.

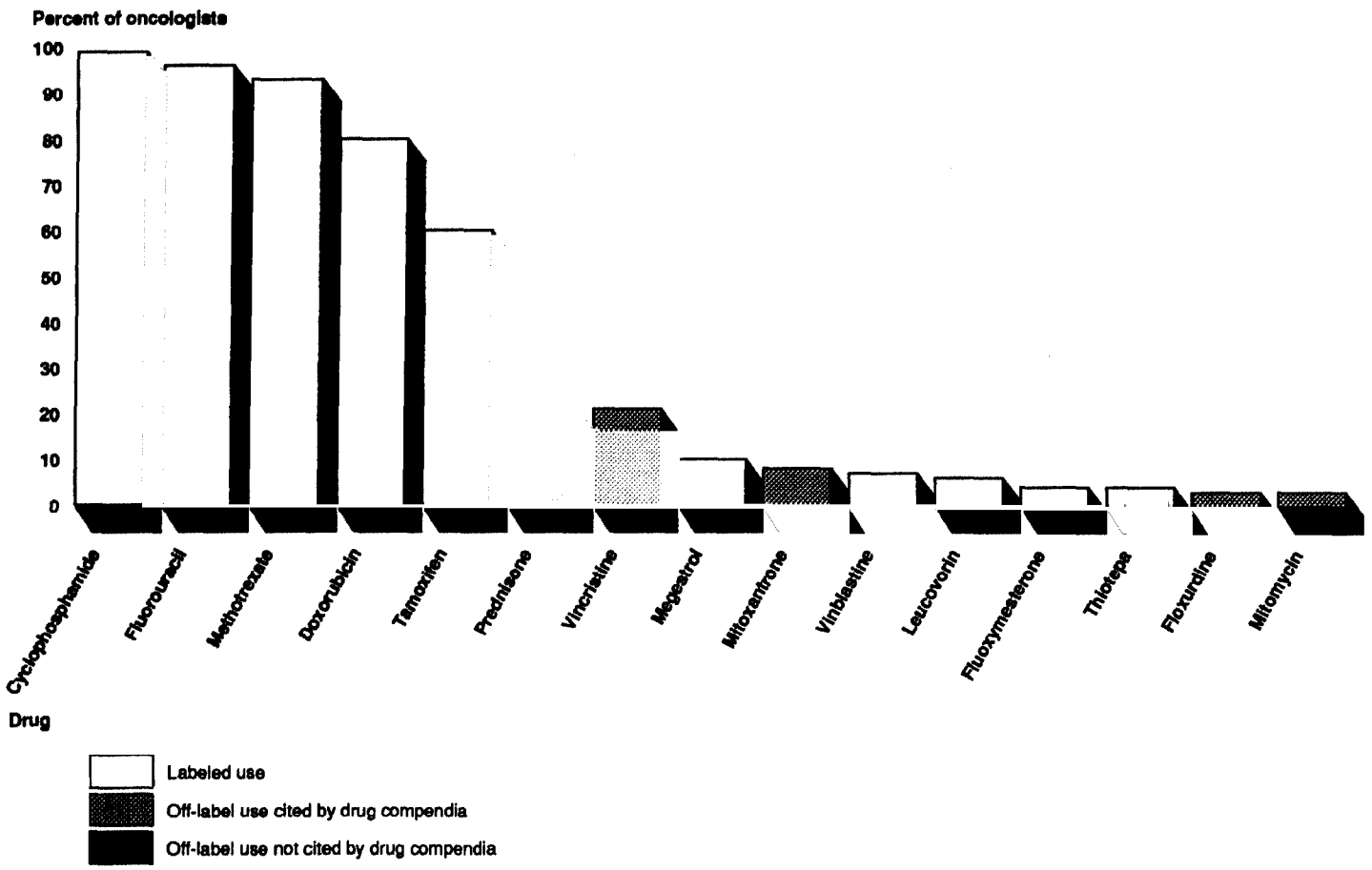
For each drug, we identified whether it was used according to its approved label, used in a way cited in the drug compendia, or used in a way that currently is not cited in these sources. In addition to a maximum of 15 drugs that appear in each figure, we note how many other drugs were reported by fewer oncologists as frequently used by them. These additional drugs do not include reported investigational drugs. However, in some cases we note some investigational drugs that a significant number of oncologists reported using frequently. For example, at the time of this survey, levamisole was classified as a treatment investigational new drug by the FDA, but it was the second most frequently used drug to treat Duke's C colon cancer.

Figure III.1: Drug Use in the Treatment of Acute Nonlymphocytic Leukemia



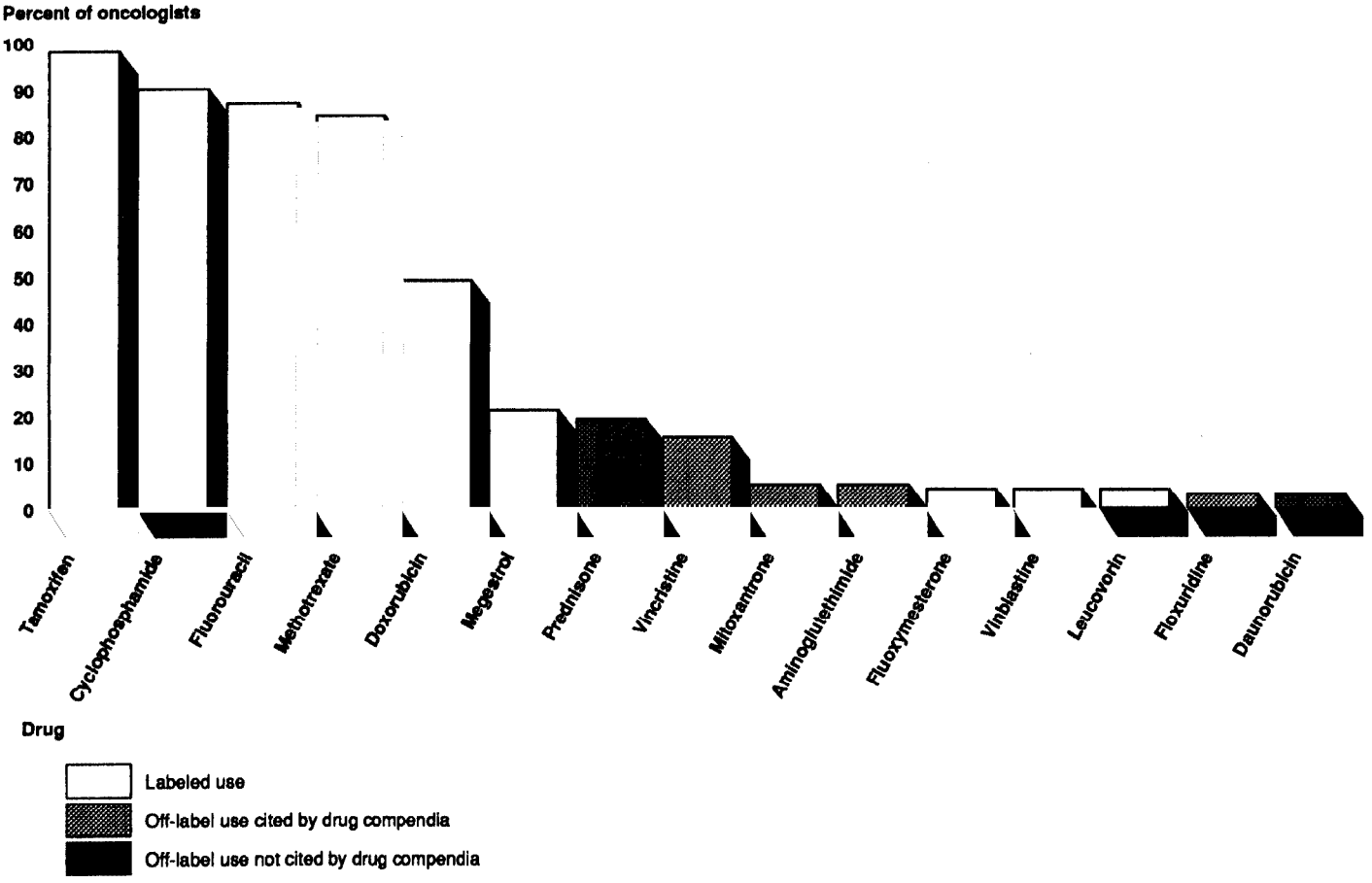
Note: Less than 2.3 percent of the oncologists reported frequent use of 17 additional drugs: 2 for on-label uses, 1 for an off-label but compendium-cited use, and 14 for off-label uses not cited in the drug compendia. In addition to FDA-approved drugs that were used, oncologists reported frequent use of 7 investigational drugs, particularly M-ASMA, which was frequently used by about 7 percent of the oncologists.

Figure III.2: Drug Use in the Treatment of Localized Breast Cancer in Premenopausal Women



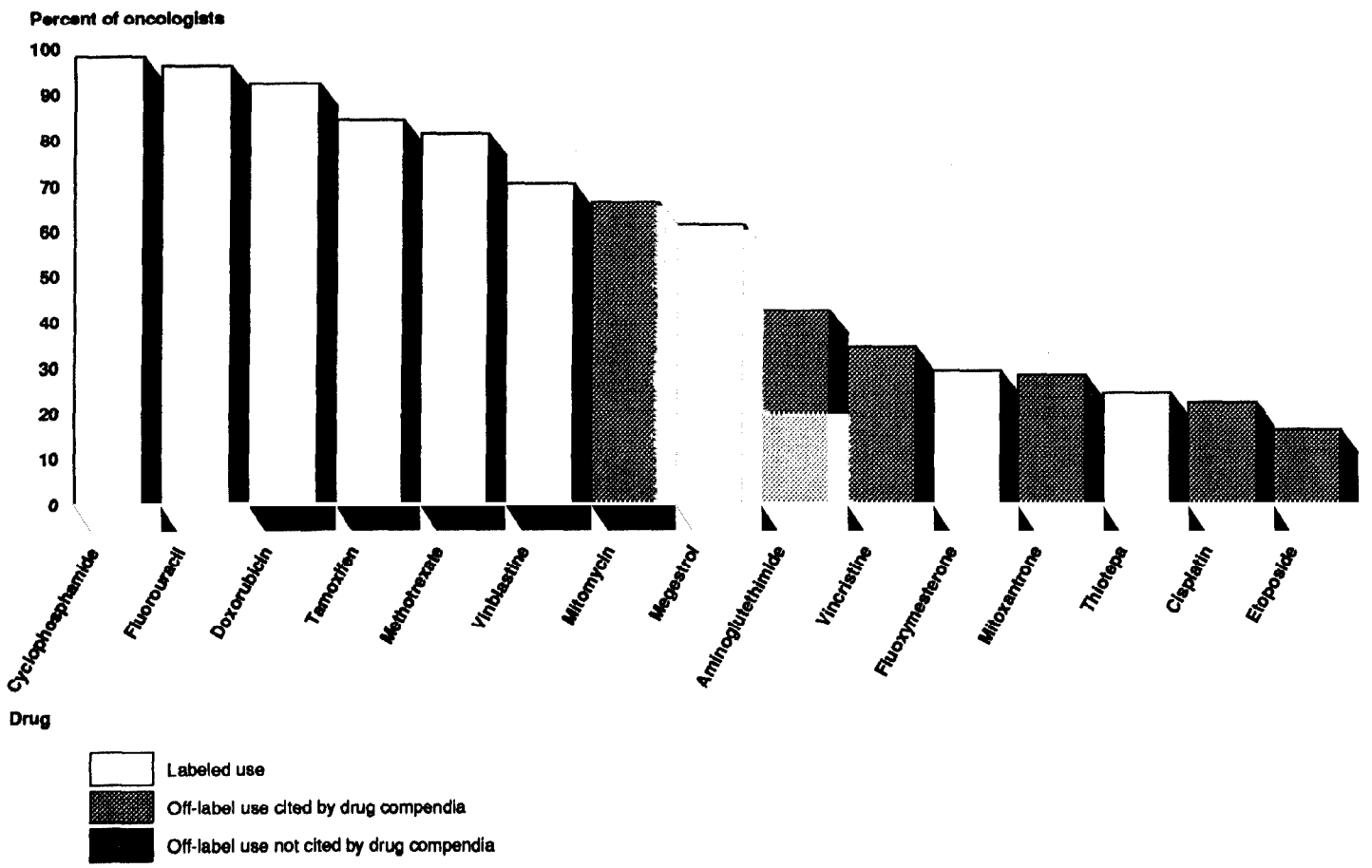
Note: Less than 3 percent of the oncologists reported frequent use of 13 additional drugs: 4 for on-label uses, 4 for off-label but compendium-cited uses, and 5 for off-label uses not cited in the drug compendia.

Figure III.3: Drug Use in the Treatment of Localized Breast Cancer in Postmenopausal Women



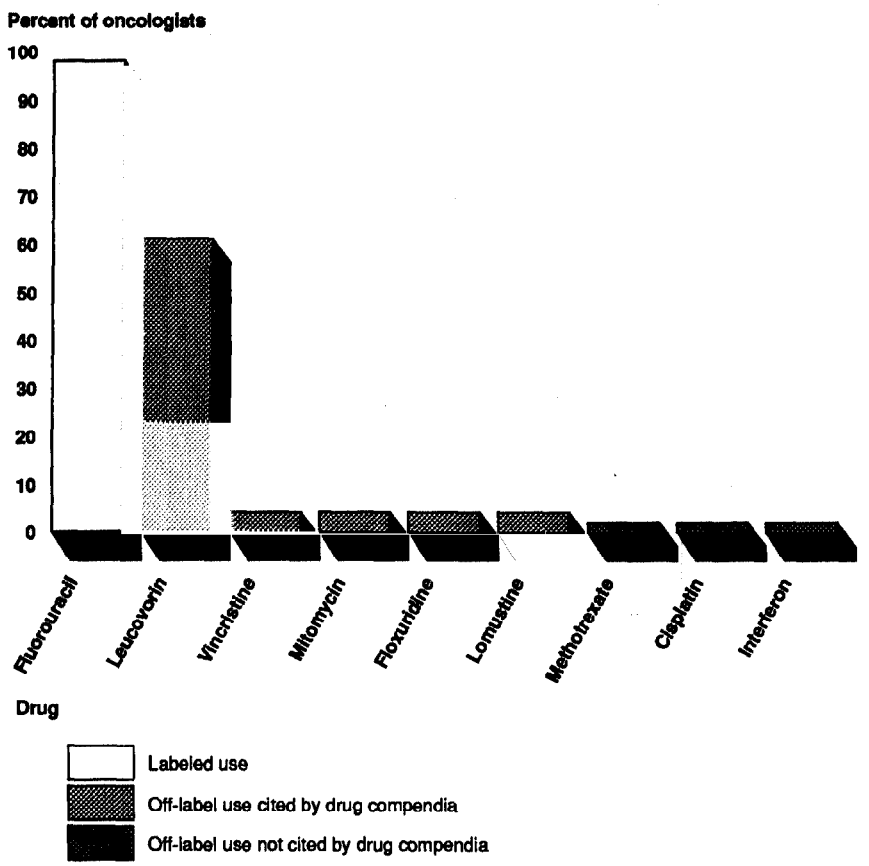
Note: Less than 3 percent of the oncologists reported frequent use of 21 additional drugs: 6 for on-label uses, 7 for off-label but compendium-cited uses, and 8 for off-label uses not cited in the drug compendia.

Figure III.4: Drug Use in the Treatment of Metastatic Breast Cancer



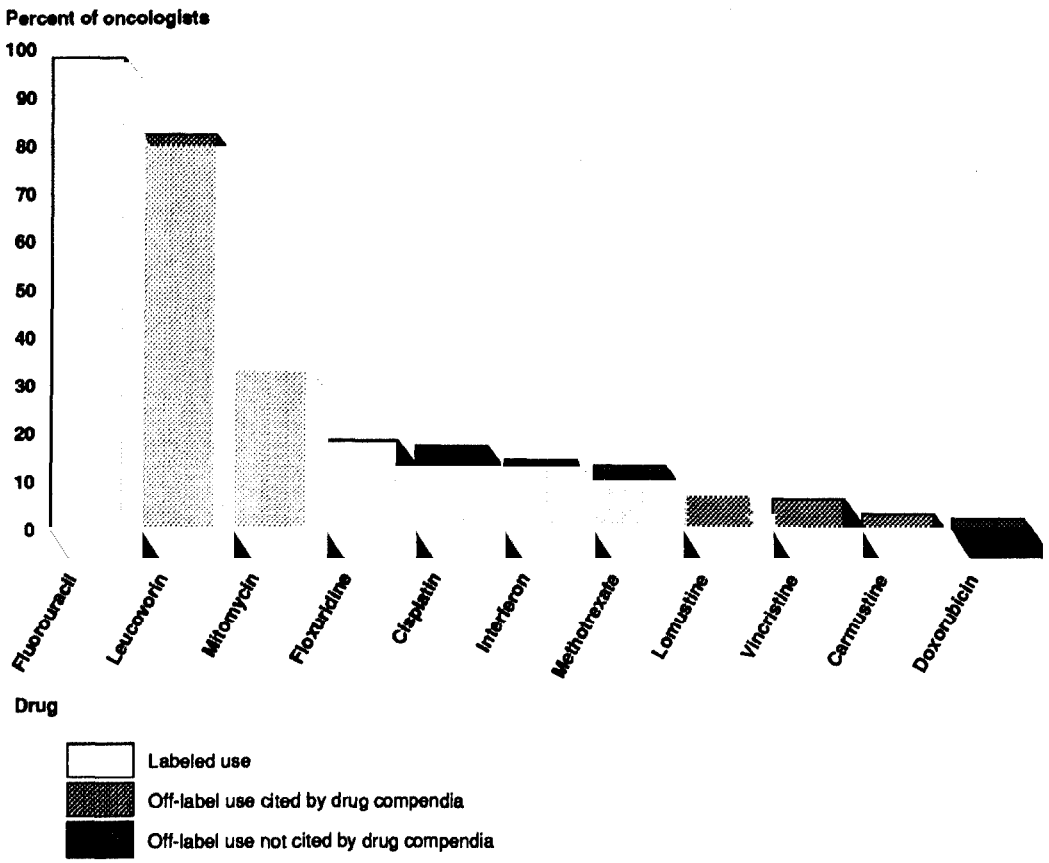
Note: Less than 16 percent of the oncologists reported frequent use of 32 additional drugs: 6 for on-label uses, 8 for off-label but compendium-cited uses, and 18 for off-label uses not cited in the drug compendia.

Figure III.5: Drug Use in the Treatment of Limited (Duke's C) Colon Cancer



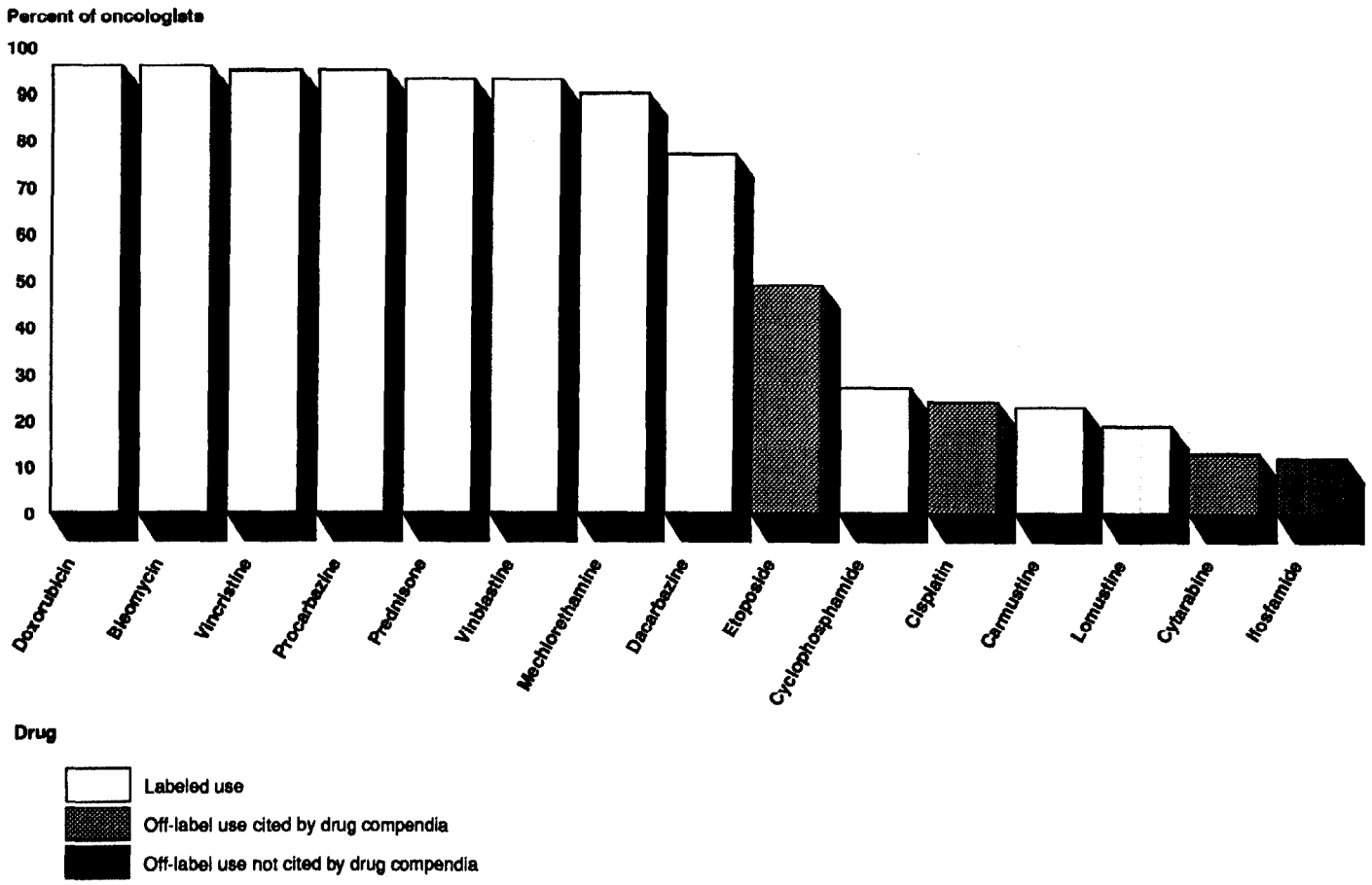
Note: Less than 1 percent of the oncologists reported frequent use of 10 additional drugs: 1 for an on-label use, 3 for off-label but compendium-cited uses, and 6 for off-label uses not cited in the drug compendia. About 81 percent of the oncologists indicated that they frequently used the investigational drug "levamisole." At the time of our survey, levamisole was available as a treatment investigational new drug in conjunction with fluorouracil as an adjunct to surgery. It has now been approved for treating colon cancer.

Figure III.6: Drug Use in the Treatment of Metastatic Colon Cancer



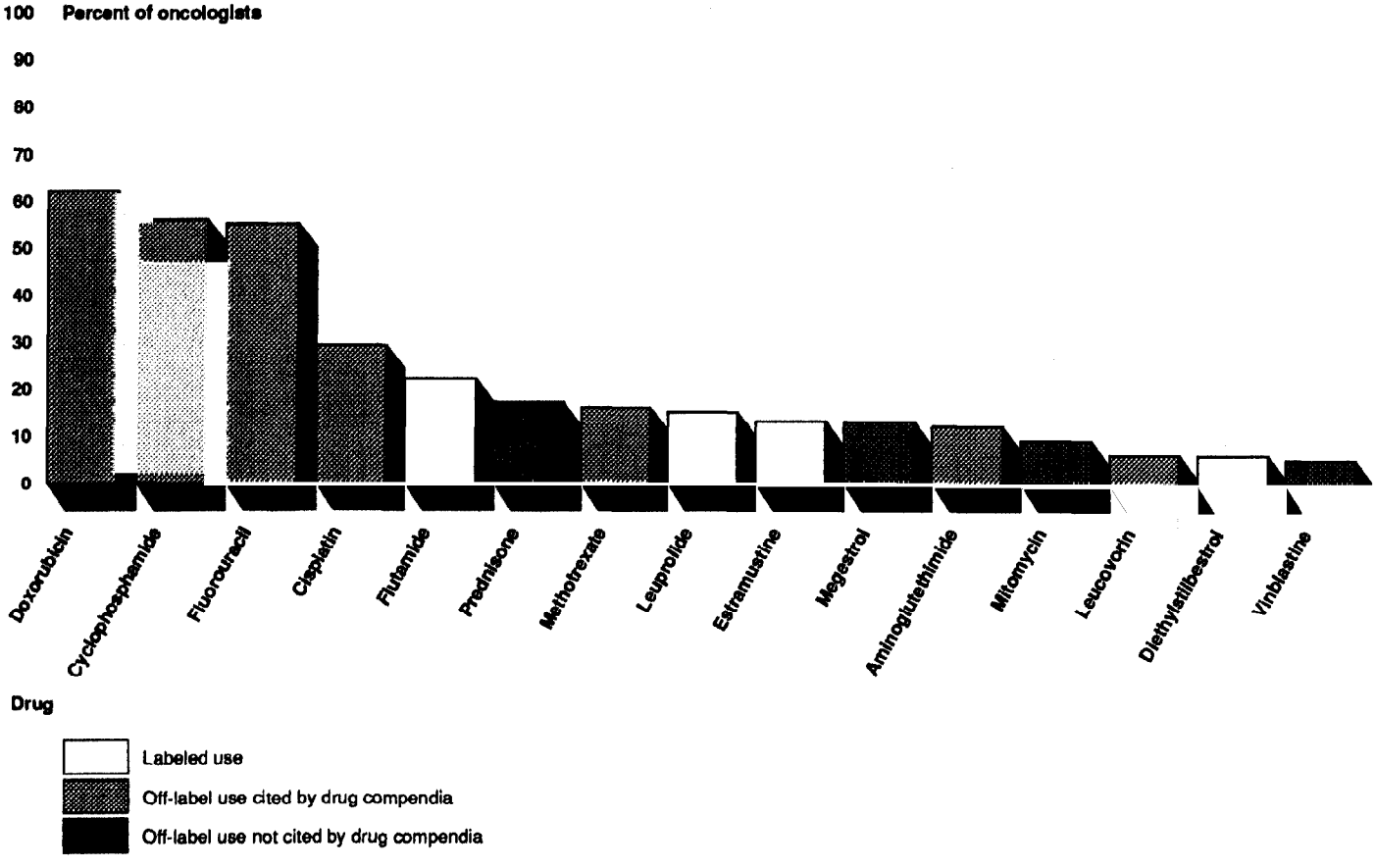
Note: Less than 1.5 percent of the oncologists reported frequent use of 15 additional drugs: 1 for an on-label use, 2 for off-label but compendium-cited uses, and 12 for off-label uses not cited in the drug compendia. About 6 and 3 percent of the oncologists indicated that they frequently used the investigational drugs levamisole and interleukin, respectively, in treating this cancer. At the time of our survey, levamisole was available as a treatment investigational new drug in conjunction with fluorouracil as an adjunct to surgery. It has now been approved for treating colon cancer.

Figure III.7: Drug Use in the Treatment of Hodgkin's Disease (Stages IIIb, IVa, or IVb)



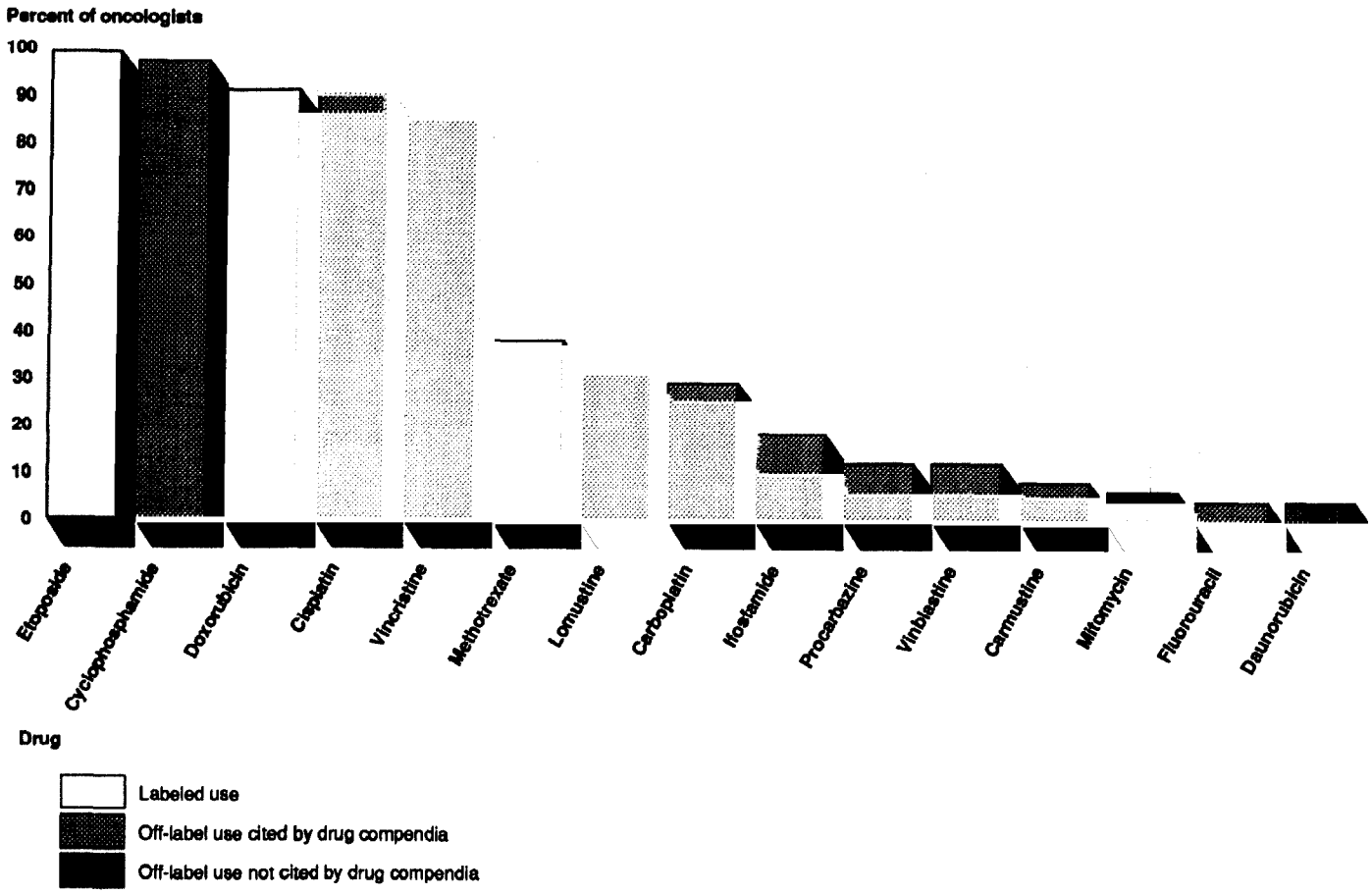
Note: Less than 11.5 percent of the oncologists reported frequent use of 37 additional drugs: 5 for on-label uses, 1 for an off-label but compendium-cited use, and 31 for off-label uses not cited in the drug compendia. About 3 percent of the oncologists indicated that they frequently used bone marrow transplants in treating this cancer.

Figure III.8: Drug Use in the Treatment of Hormone Refractory Prostate Cancer



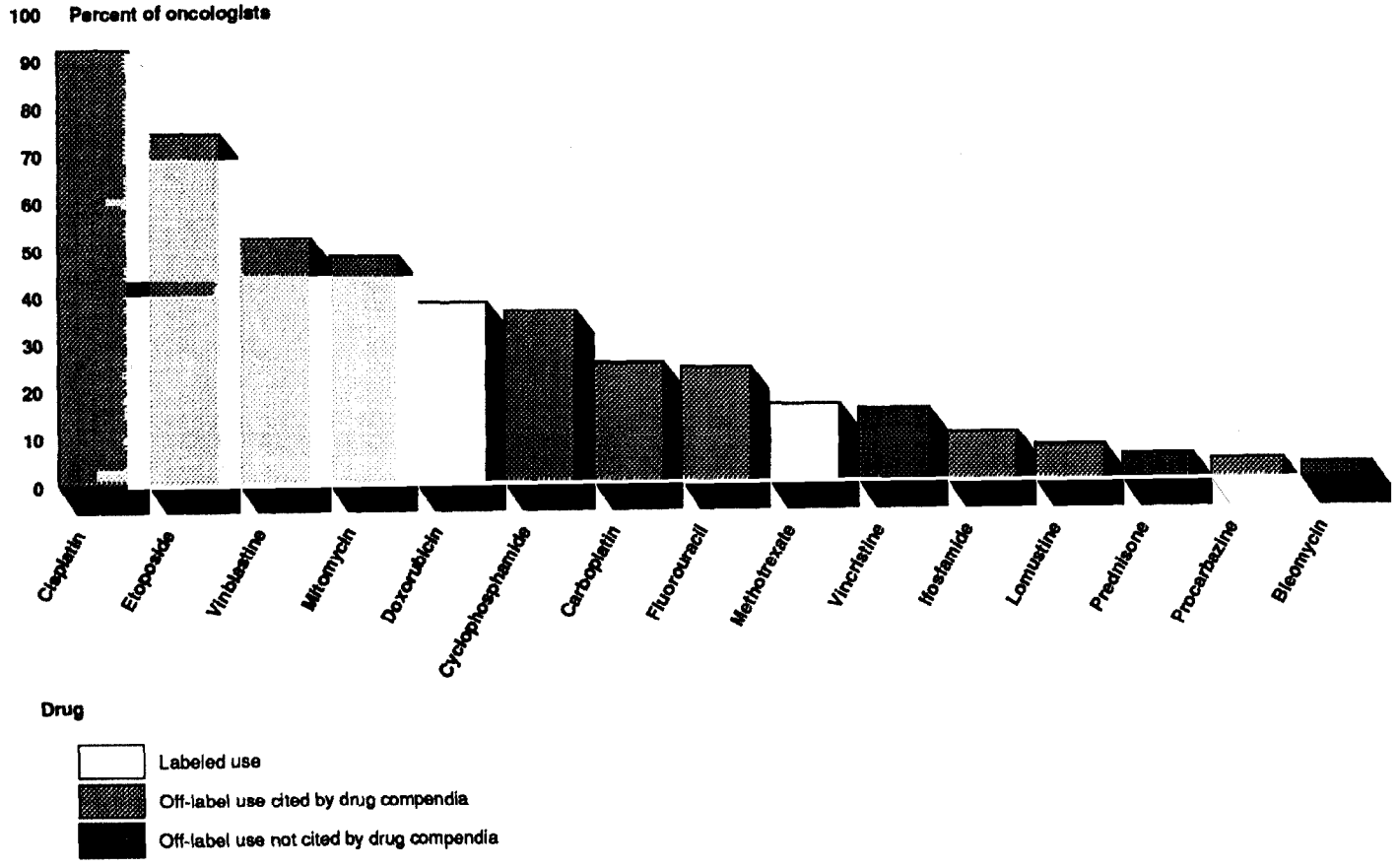
Note: Less than 5 percent of the oncologists reported frequent use of 24 additional drugs: 3 for on-label uses, 4 for off-label but compendium-cited uses, and 17 for off-label uses not cited in the drug compendia.

Figure III.9: Drug Use in the Treatment of Small Cell Lung Cancer (Limited and Extensive)



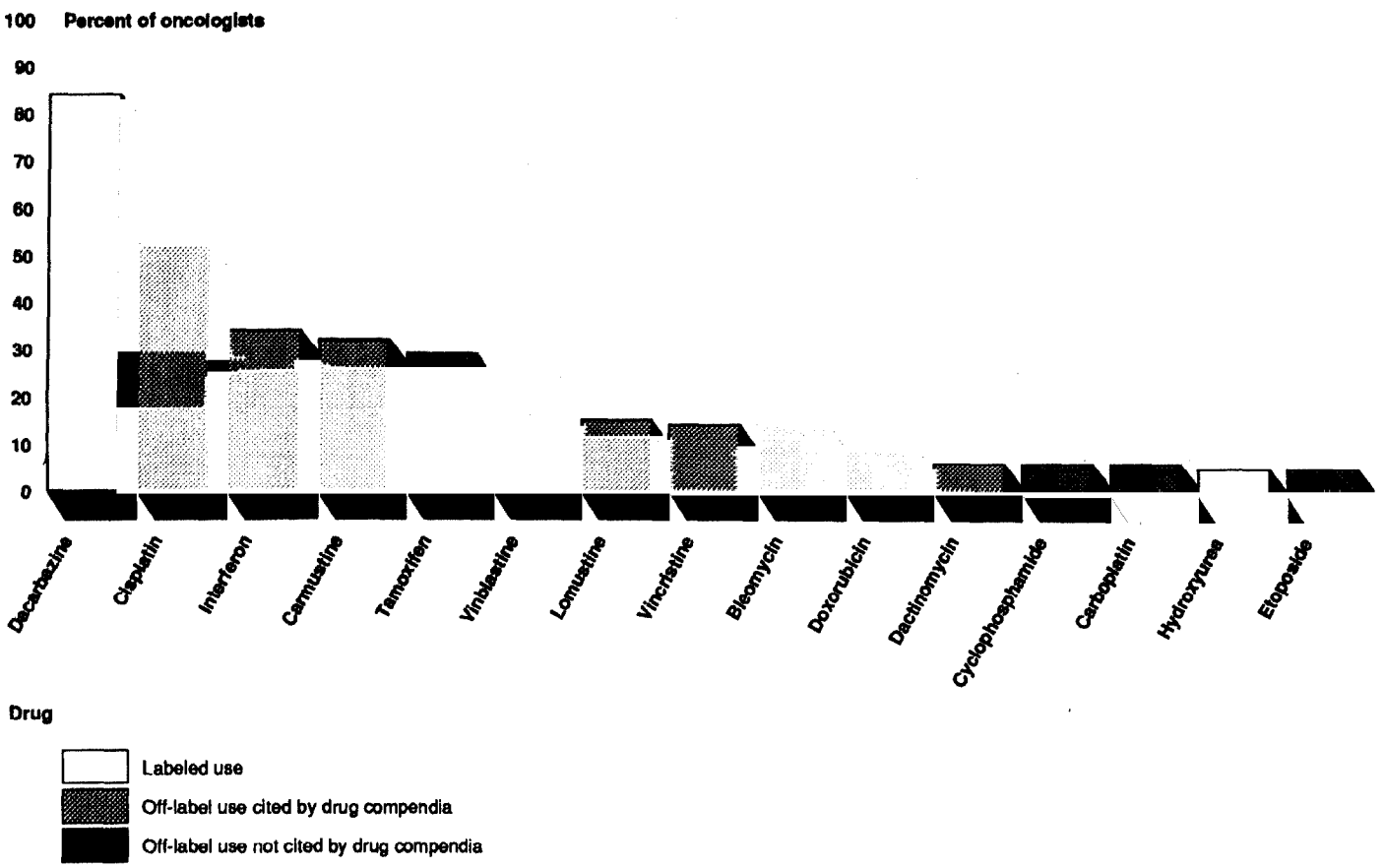
Note: Less than 4 percent of the oncologists reported frequent use of 35 additional drugs: 2 for on-label uses, 2 for off-label but compendium-cited uses, and 31 for off-label uses not cited in the drug compendia.

Figure III.10: Drug Use in the Treatment of Non-Small Cell Lung Cancer



Note: Less than 3 percent of the oncologists reported frequent use of 17 additional drugs: 2 for on-label uses, 4 for off-label but compendium-cited uses, and 11 for off-label uses not cited in the drug compendia.

Figure III.11: Drug Use in the Treatment of Malignant Melanoma



Note: Less than 2.5 percent of the oncologists reported frequent use of 23 additional drugs: 2 for off-label but compendium-cited uses, and 21 for off-label uses not cited in the drug compendia. About 26 percent of the oncologists indicated that they frequently used the investigational drug interleukin in treating this disease.

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