AUDIT INDICATES HALF OF CURRENT CHEMOTHERAPY USES LACK FDA APPROVAL

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Many oncology practitioners, pharmaceutical manufacturers, and health care administrators are becoming increasingly concerned about recent attempts by third-party payors to enforce long-standing contract provisions that would deny payment for unlabeled chemotherapy drugs---that is, drugs used for indications that do not fall within the package insert guidelines approved by the Food and Drug Administration (FDA). To help concerned parties understand the payment implications of this health policy proposal, an audit of patient records was conducted to determine the prevalence of unlabeled drug use in oncologists' private practices, and to estimate the level of payment shortfalls providers' would be likely to face if insurers were to deny payment for such treatments. (See "How the Audit Was Conducted" on page 24.)

In 1986, the medical records of cancer patients who had received chemotherapy in a private-practice setting during the first six months of that year were audited. The following discussion profiles the volume of unlabeled usage and the resultant potential loss in third-party payments for eight commonly prescribed chemotherapy drugs: Adriamycin, Cytoxan, Fluorouracil, Methotrexate, Mutamycin, Oncovin, Platinol, and Vepesid.

ADRIAMYCIN

Adriamycin, a frequently used agent with broadly defined indications, is often used in difficult-to-treat solid tumors. Gastrointestinal/digestive cancers make up the majority of out-of-package insert use of Adriamycin. Total out-of-package insert use for this agent accounts for fifteen (15) percent of all use. (See Table 1 for a summary of out-of-of-package use by diagnosis, projected number of patient treatments, and percentage of unlabeled use.)

CYTOXAN

Cytoxan shows extensive use as a single agent, but is more frequently used in combination with other cytotoxic drugs. As is the case with Adriamycin, the majority of outside-of-labelling use is for difficult-to-treat solid tumors. Lung cancers and gastrointestinal malignancies are the leading out-of-package insert uses for Cytoxan. About 22 percent of Cytoxan use falls outside of FDA-approved indications.

FLUOROURACIL

Fluorouracil, a relatively inexpensive product, is widely used, but only a small percentage (4 percent) of its uses are for out-of-package insert indications. Lung cancer and prostatic cancer are the two most common unlabeled uses. This agent has been on the market for more than 20 years and, at this point, little in the way of new clinical literature is being developed. As a result, non-FDA approved uses have little support. However, the dollar impact for this agent is minimal compared to newer, more expensive chemotherapy agents.

METHOTREXATE

Like Fluorouracil, out-of-package insert use of Methotrexate is minimal---only 12 percent of use falls outside of package labeling. This agent also is relatively inexpensive, which minimizes the financial impact of non-approved use. Gastrointestinal cancers account for the highest percentage of out-of-package insert use of Methotrexate, which is almost always used in combination with other agents. The package insert implies a wide range of applications in the "palliative and managed care" of several malignancies. This choice of wording makes the package insert definition less clear. None of these uses were

TABLE 1

OUT-OF-PACKAGE INSERT USE FOR EIGHT COMMON CHEMOTHERAPY AGENTS

Agent	Unlabeled Diagnoses	1986 Projected Treatments	1986 Percent Unlabeled Use
Adriamycin	G.I./Digestive Cancers	68,182	
	Other Malignancies	36,444	15%
Cytoxan	G.I./Digestive Cancers	5,972	
	Lung Cancers	182,384	
	Other Malignancies	30,200	22%
Fluorouracil	Lung Cancers	33,310	
	Metastatic Adenocarcinoma	12,584	
	Metastatic Prostate Cancer	23,650	4%
Methotrexate	G.I./Digestive Cancers	72,834	
	Ovarian Cancers	18,912	
	Other Malignancies	28,688	12%
Mutamycin	Rectal Cancers	56,364	
	Lung Cancers	16,782	
	Breast Cancers	82,200	
	Ovarian Cancers	3,420	
	Other Malignancies	12,142	84%
Oncovin	G.I./Digestive Cancers	16,132	
	Breast Cancers	133,348	
	Lung Cancers	151,304	
	Other Malignancies	71,900	41%
Platinol	G.I./Digestive Cancers	7,528	
	Lung Cancers	38,344	
	Metastatic Thyroid Cancer	4,336	
	Malignant Melanoma	2,580	
	Metastatic Uterine Cancer	3,432	
	Other Malignancies	34,596	68%
Vepesid	G.I./Digestive Cancers	2,540	
	Ovarian Cancers	4,556	
	Brain Cancer	660	
	Hematologic Malignancies	33,722	31%

considered in this study as outside labeling, but, in fact, may well be considered such under more stringent guidelines.

MUTAMYCIN

The data for Mutamycin indicate that the majority of its uses fall outside of labeling (84 percent). Because Mutamycin is a costly drug, the financial impact of such a large percentage of non-FDA approved usage is significant. As with most of the other agents' non-approved uses, Mutamycin's primary application is in the treatment of solid tumors for which there is no other known therapeutic regimen that is effective. Breast cancer is the most frequent unlabeled diagnosis for which it is used, followed by rectal cancers. Both of these malignancies have universally poor prognoses.

ONCOVIN

Slightly less than half (41 percent) of Oncovin use is outside the package insert. Breast and lung cancer provide the bulk of non-approved use. Because of the high cost of this agent, the financial significance is profound. As with other agents, the most resistant malignancies are the diagnoses for which Oncovin is used outside of labeling.

PLATINOL

Platinol, one of the most frequently used antineoplastic agents, displays broad usage outside of the package insert. Sixty-eight (68) percent of Platinol treatments are for solid malignancies, such as lung cancers, which are not FDA-approved indications. This product is relatively expensive, and consequently, has a significant financial impact.

VEPESID

Vepesid, which only recently was approved for the treatment of small cell lung cancer, is used outside of package insert guidelines thirty-one (31) percent of the time. However, if lung cancer had not been recently approved as an indication, more than sixty (60) percent of use would have been outside of labeling. This is an excellent example of the establishment of a "standard of medical practice" prior to an actual FDA-approved indication.

CHEMOTHERAPY SALES: 1984-1986

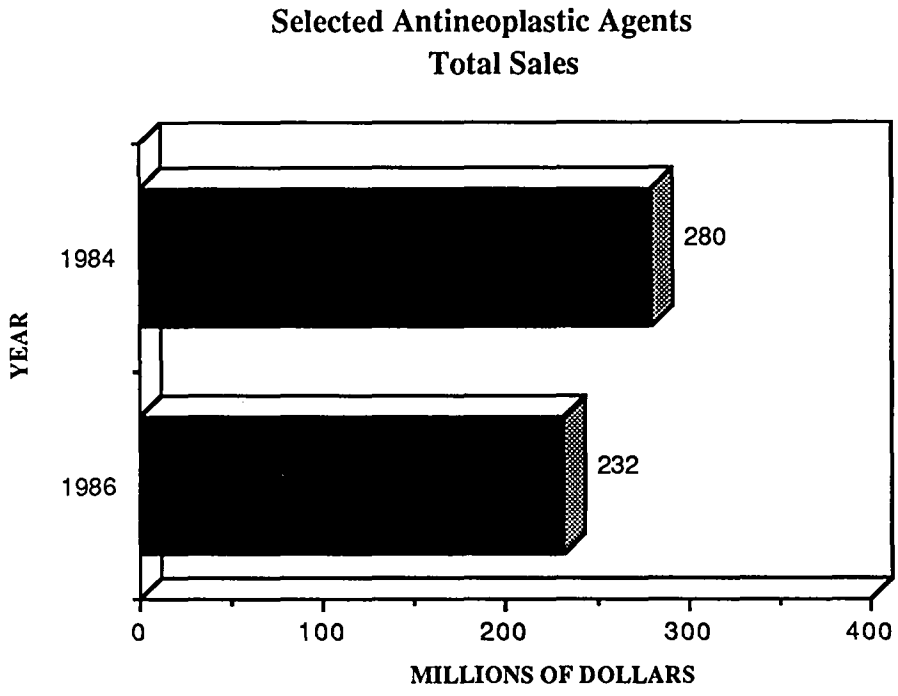
The data in the previous section provide documentation regarding the percentage of use outside the package insert. This section provides the actual sales data to which these percentages can be applied. The financial impact of the eight drugs for which non-FDA approved uses were studied is significant. Although the dollars presented in this section are not to be considered absolute, it is evident that several million dollars in annual sales for a given agent come from its use outside of package insert indications. In fact, these data are for audited sales only, which may understate the actual volume due to the exclusion of wholesale cytotoxic drug sales, and other unreported transactions.

"The antineoplastic market alone increased from $357 million in 1984 to $448 million in 1986."

There is little doubt that the cancer market is growing. The antineoplastic market alone increased from $357 million in 1984 to $448 million in 1986. This impressive growth rate of 20 percent per year is due to the recent introduction of newer, more expensive agents, as well as the increased use of existing agents in new drug combinations and for diverse new indications. Because of the dramatic growth in clinical literature for all chemotherapy agents, increased public awareness of neoplastic disease, and the expansion of the hematology/oncology speciality, this market is expected to continue at a solid rate of growth in future years.

In terms of the antineoplastic agents reviewed in this study, sales have grown from $232 million in 1984 to almost $280 million in 1986. All products have displayed increased sales, with the exception of Fluorouracil. The largest gains recorded are for newer agents and/or those with an expanding literature base or claim structure (i.e., Vepesid). A summary of total sales for the eight agents reviewed in

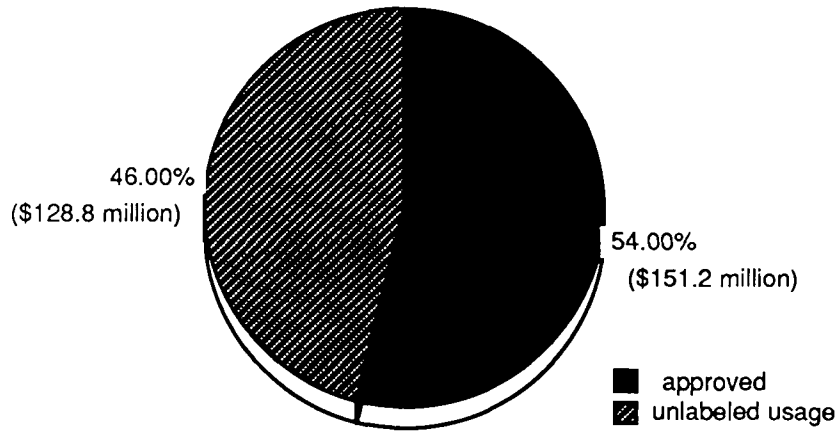
FIGURE 1



*The data presented reflect audited sales only; actual sales volume may be understated due to nonrepresentation in the audit of certain oncology specialty product distributors.

FIGURE 2

1986
Percentage and Total Annual Sales of Approved versus Unlabeled Usage of Eight Common Chemotherapy Drugs



this study for the years 1984 through 1986 appears in Figure 1.

If the data regarding percentage of use outside the package insert that were obtained for the eight chemotherapy agents are applied to the annual sales of these products, it is possible to predict the actual financial impact of non-approved use.

Products that have established use, such as Fluorouracil, and are less expensive than more recently developed products, such as Vepesid or Platinol, show less use outside the package insert and, consequently, a reduced financial impact. Mutamycin and Platinol, which have the largest percentage of use outside FDA labeling, show the greatest financial impact. Platinol had more than $45 million in estimated sales outside of the package insert. For the reviewed agents, 46 percent of total sales are for uses outside of FDA-approved indications. (See Figure 2.)

HOW THE AUDIT WAS CONDUCTED

This comprehensive oncology study, designed to quantitate the use of conventional chemotherapy by diagnosis, was completed in 1986. The methodology used was a study of approximately 3,500 medical records for patients who received chemotherapy during the six-month period of January through June 1986.

The sample was drawn from the private practice records of 165 oncologists. (To avoid physician bias, the data were obtained directly from patient records.) Although the absolute dollar value assigned to these agents may not have the statistical confidence level of sales audits (see "Chemotherapy Sales for 1986," above), it documents the extent of chemotherapy use outside of FDA-approved package insert guidelines during the above six-month period.

This study provides documentation of the uses of antineoplastic agents. It was designed to be comprehensive in its provision of qualitative and quantitative market research in the areas of antineoplastic use outside of package insert indications. Because this is a dynamic, changing area, however, the parameters and data provided require revision in the coming months and years. It is obvious that the issues addressed in this study touch many individuals at many levels, and are larger in scope than any one company or product. ■

SUMMARY

On the basis of this study, it is apparent that physicians commonly prescribe antineoplastic agents for indications outside FDA-approved uses. The financial implications of such practices are significant and, for the eight leading agents reviewed in this study, represent almost half of their total annual sales.

The percentage of non-approved use varies for each agent, from as low as 4 percent for fluorouracil to 84 percent for Mutamycin. This tends to correlate to the amount of ongoing clinical research, as well as the time since product introduction. The non-approved malignancies are predominately those with a poor prognosis and very little approved alternate therapy, (i.e., lung, bowel, and breast cancer).

Private insurers, rather than government (Medicare) represent the greatest opportunity for the advancement of payment for unlabeled uses of chemotherapy. At present, however, there is only about a 70 percent overall rate of payment for antineoplastic agents used outside of the package insert. Nevertheless, there is no indication that a liberalization in payment for antineoplastic use outside the package insert would result in an overwhelming financial burden for providers. On the contrary, physicians indicate that under such circumstances they would increase use, but only at a prudent level that would parallel the development of clinical literature.

However, the mechanism to establish a "standard of medical practice" remains unclear and additional research is needed. For instance, in the case of Vepesid, its documented effectiveness in treating small cell lung cancer led to wide use of the product for that malignancy. In the past two years, this indication for use has become a "standard of medical practice" and, more recently, was approved by the FDA. If uses for other agents have sufficient clinical documentation, the classification of "standard medical practice" may be achieved through the American Medical Association (AMA), the Association of Community Cancer Centers (ACCC), or other medical organizations. This recognition may augment any argument for increased payment. ■

In the Spring issue of the Journal, a similar study about the current labeled versus unlabeled uses of combination chemotherapy will be published.

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