The Oncologist’s Impact on Drug Choices

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The Controversy

Over the past 20 years, obtaining reimbursement for “off-label” use of drugs has become more reliable due to changes in the law and Medicare policy, and the work of physician organizations. Because much of cancer treatment is off-label, these changes have major implications for oncology physicians and their patients.

Specifically, the current process of identifying medically accepted standards for off-label use of drugs has increased attention on the drugs used for cancer treatment. The process for off-label approval is now more responsive in part because of the central role NCCN has played in defining the standard of care for cancer treatment and the inclusion of the NCCN Drugs & Biologics Compendium (NCCN Compendium) in the recognized authoritative compendia used in Medicare to determine “medically accepted indications,” including off-label use, in an anticancer chemotherapeutic regimen.

What Is Off-Label Drug Use?

When the FDA is satisfied that a drug works and is safe, the FDA and the drug manufacturer create the drug “label,” which is a report containing very specific information about the drug. The drug label provides information about the drug and its approved uses, including approved doses, patient population, and medical condition for which it was approved. Using a drug differently from what is described in the FDA-approved label is considered “off-label” use. This can mean that the drug is

- Used for a different disease or medical condition,
- Given in a different way (such as by a different route) or different regimen, or
- Given to a different patient population or in a different dose.

For example, when a chemotherapy drug approved for treating cancer A is used to treat cancer B, use with cancer B would be off-label use. Off-label is also called “non-approved” or “unapproved” use of a drug.

Is Off-Label Drug Use Legal?

The off-label use of FDA-approved drugs is legal in the United States and many other countries, with the exception of some controlled substances, such as opioids (pain medicines such as morphine and fentanyl). These drugs cannot legally be prescribed in the United States except for approved purposes.

However, although doctors can legally use drugs off label, drug companies cannot legally market drugs for off-label uses. This has been a hot news topic recently, because drug companies have been fined for promoting drugs for uses not FDA-approved. Off-label marketing is very different from off-label use.

Is Off-Label Use Regulated?

The FDA does not regulate the practice of medicine. Therefore, in general, after a drug is approved by the FDA, licensed doctors can use it for any purpose they consider medically appropriate. Off-label use can vary greatly from one doctor to another, depending on the doctor’s preferences, knowledge, and past patient experiences.

How Common Is Off-Label Drug Use?

Off-label drug use is well-documented and very common in certain settings, such as pediatrics, HIV/AIDS care, and cancer treatment. In 1991, a General Accounting Office (GAO) study reported off-label use of anticancer drugs as high as 33%. In 2007, an NCCN
study found that number had reached 50% to 75% of all uses of anticancer therapy.\textsuperscript{3} A study performed in 2008 found that 8 of 10 oncologists surveyed had used drugs off-label.\textsuperscript{4}

The NCI has stated, “Frequently, the standard of care for a particular type or stage of cancer involves the off-label use of one or more drugs.” Actual off-label use is likely much higher because chemotherapy is only one aspect of cancer treatment. Studies have yet to look at off-label use of other drugs in cancer treatment, such as antinausea drugs and pain medicines.

**Why Are Drugs Used Off-Label?**

Older, generic medicines are the drugs most often used off label, because clinicians have discovered new uses for them. New uses are often reported in the medical literature, with clinical studies to support them, but the use remains “off-label” because the makers of those drugs have not put them through the formal, lengthy, and often costly studies required by the FDA to officially approve a drug for new uses.

Reasons for the high off-label use in cancer treatment are familiar and include lack of approved treatment regimens or failure of approved regimens for some patients and lack of FDA-approved treatments for rare cancers. In addition, advances in cancer research often outpace the FDA approval process. Cancer treatment is always changing and improving. Finally, lack of approved therapy in the face of terminal illness is the underlying force.

**What Are the Legal Risks of Off-Label Use of Drugs?**

Another consideration in deciding to use a drug off label is the legal risk. The main legal risk is in prescribing a drug outside its labeled options should a patient have an unwanted or bad outcome from the treatment. The problem is that off-label drug use often does not reflect “standard of care” treatment.

**How Important Is Off-Label Use to Clinical Practice and Patient Outcomes?**

Off-label use of anticancer drugs has played a major part in the dramatic advances in patient survival over the years. For example, in the 1950s, nearly all children with leukemia died. Between the late 1960s and now, the treatment of leukemia has changed significantly, often through the use of off-label medications, and experts recognized that significant progress was being made. The survival rate for children in the 1980s was about 75%. Today, childhood leukemia is one of the most successfully treated cancers.\textsuperscript{5}

Equally important was what the oncology community learned from this successful achievement in cancer care. In the medical community, off-label uses often met the threshold as “accepted medical practice.” However, the existing process to recognize off-label use of drugs did not include a formal or administrative way to establish this use for purposes of coverage and payment by insurers. Obtaining payment involved work by individual physicians to prove to insurers—especially Medicare—that the use did indeed reflect “accepted medical practice.”

**Reimbursement Issues**

**Are Drugs Covered by Insurers?**

Whether an insurer will reimburse for a drug depends on whether they considered it “covered” under the law and their contract. Insurers generally cover FDA-approved drugs when their use is consistent with the FDA label and generally do NOT cover experimental drugs. Insurers have relied on a decision that the use is recognized for “medically-accepted indications” but have differed on the evidence used and how they weigh the evidence. This means that coverage of off-label use has been variable within the same insurer, state-to-state, and between insurers.

This variability presents a major problem for office staff in oncology practices, and, as many experts realize, this problem has major implications for physicians.
and patients. In a GAO study, as many as 40% of oncolgists altered their preferred treatment because of reimbursement and cost issues.

Whether an off-label use is “medically accepted” is usually decided by the individual insurer/payer at the state level. However, Medicare plays a central role in this process. For Medicare, the decision is made by the Medicare carrier, now called “contractors.” In 1989, Medicare initiated changes that helped physicians understand what would be covered and influence coverage decisions. Contractors were required to publish coverage policies. They were also required to develop Medicare medical advisory panels to involve the medical community in the process of reviewing medical literature to identify the standard of practice that would be the foundation of the local carrier coverage policies, including off-label use of drugs.

Although this process improved the situation immensely, it did not achieve enough transparency, because the more than 40 carriers in existence meant 40 different local policies. It also meant work for physicians and their associations because they had to address the same issues in each state.

**Legislation That Paved the Way to Change**

In 1993, federal legislation (OBRA) provided the impetus to create a more consistent, consolidated process to identify “medically-accepted” off-label use of drugs. OBRA required that Medicare cover off-label uses of anticancer drugs that were included in certain medical compendia: the AMA Drug Evaluations, US Pharmacopeia Drug Information (USP-DI), and American Hospital Formulary Service Drug Information (AHFS-DI).

In 2003, this approach was required for Part D drugs as well.

Over time, however, several of these compendia ceased publication, until only the AHFS-DI was being published. Stakeholders (physicians) asked Medicare to exercise its prerogative as allowed in the law to revise the list to include currently recognized authoritative compendia.

Medicare commissioned the Agency for Healthcare Research and Quality (AHRQ) to summarize how anticancer drugs are added to the various compendia and make recommendations for a new list of authoritative compendia, for presentation in March 2006. AHRQ commissioned the Duke Evidence-Based Practice Center and the Tufts-New England Medical Center to jointly prepare a report for Medicare. For each compendia, they examined the publication criteria, the breadth of listings, the speed of throughput, the published criteria and process used, public transparency in the evaluation process, public notification of conflicts of interest, and funding sources of the compendium and its parent organization. For the drugs and biologics, they looked at the level of detail of evidence reviewed, the type of recommendations and any bias (eg, “recommend,” “not recommend,” or silence), and the inclusion of analysis of potential harms and benefits, including the quantification of components used. They focused on 14 anticancer combinations that reflected newer and older agents, common and rare cancers, and biologics and drugs, and compared recommendations in the existing compendia to each other and to their own review of the evidence.

The new list of recognized authoritative compendia is

- AHFS-DI,
- NCCN Compendium,
- Thomson Micromedex DrugDex, and
- Clinical Pharmacology.

Medicare provided further information for the local policy decisions and for the medical community. They noted that the listed compendia use different rating and recommendation systems that may not be readily cross-walked from compendium to compendium. They instructed the Medicare contractors in MLN #6191 that an
off-label use is identified by a compendium as medically accepted if

- The indication is Category 1 or 2A in NCCN or Class I, IIa, or IIb in DrugDex, or
- Narrative text in AHFS-DI or Clinical Pharmacology is “supportive.”

A use is not medically accepted by a compendium if the

- Indication is Category 3 in NCCN or Class III in DrugDex, or
- Narrative text in AHFS or Clinical Pharmacology is “not supportive.”

What if an Off-Label Use Is Not Included in the Compendia?

Medicare contractors may also identify off-label uses that are supported by clinical research in peer-reviewed medical literature. This may appear in scientific, medical, and pharmaceutical publications in which original manuscripts are published. The research should have been critically reviewed for scientific accuracy, validity, and reliability by unbiased, independent experts prior to publication. They are not to consider abstracts (including meeting abstracts) and in-house publications of entities whose business relates to the manufacture, sale, or distribution of pharmaceutical products.

Medicare instructions for their contractors are that when evaluating this literature, Medicare contractors will consider (among other things)

- Whether the clinical characteristics of the beneficiary and the cancer are adequately represented in the published evidence,
- Whether the administered chemotherapy regimen is adequately represented in the published evidence,
- Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients, and
- Whether the study is appropriate to address the clinical question.

Conclusions

The long and short of it for insurers/payers, physicians, and patients is that rapid inclusion of indications for anticancer drugs in a compendium takes the least amount of effort and time for verifying whether a drug should be covered for the off-label use, which translates into it being reimbursed. Because of the timely review of new off-label uses for inclusion in the NCCN Compendium, participation in the NCCN process provides an excellent opportunity for oncologists to expedite the process of getting new “off-label” uses covered as a medically accepted indication not only for their patients, but for all patients.

References