

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

## Off-Label Drug Utilization in Oncology

Jonas A. de Souza, MD  
Instructor of Medicine  
Section of Hematology/Oncology  
University of Chicago Medical Center  
Chicago, Illinois

### H&O What is the definition of off-label drug utilization?

**JD** There are 3 ways of prescribing drugs in oncology: on-label, off-label, and off-evidence. The official labeling on a drug lists a specific indication for the antineoplastic agent on the basis of findings from clinical trials. Marketing authorizations are granted by the US Food and Drug Administration (FDA) if the drug is judged to be safe and effective for that specific indication at the specific dosage and administering method. Any other indication for use of this drug is considered off-label. The use of an off-label drug can further be distinguished between: (1) off-label use that can be supported by scientific evidence or (2) use when there is little clinical evidence or lack of scientific rationale. The latter use can be considered off-evidence use. Prescribing a drug that is still under investigation in a clinical trial can also be considered off-evidence when done outside that specific study.

### H&O Why is off-label drug use more frequent in oncology?

**JD** An estimated 50% of cancer care is off-label, and there are several reasons for this. First, in order to obtain the FDA approval or label, the manufacturer has to apply for it based on the available evidence. However, if the drug is already widely adopted in practice, there is no financial incentive for the drug company to pursue this process. Second, it is not always feasible to have a

phase III clinical trial for rare or uncommon tumors statistically powered to identify an overall survival benefit. Limited evidence from phase II trials may demonstrate benefit of agents in these cases, and the drugs may be adopted in practice in an off-label way. Third, there is usually a period between positive clinical trial results, either published or reported at professional meetings, the manufacturer's application for FDA labeling, and the actual FDA-approval. By definition, if this drug is being adopted by clinicians after dissemination of positive clinical trial results and before FDA approval, this drug is being utilized in an off-label way. These are all off-label uses justified by evidence. It is also common for drugs in oncology to have a wide range of activities with biologic plausibility, but at the same time to have a specific indication or dose regimen based on the clinical trial that led to FDA approval for a specific disease. Anything outside that indication or dose is also considered off-label. Oncologists and cancer patients are also more willing to try drugs with little evidence in the advanced or metastatic setting outside of clinical trials in the hope that these drugs may provide better results, such as prolonging life. Also, there may be emotional and financial factors to keep pursuing off-evidence treatments.

### H&O Are there any benefits to off-label drug use, and when is there justification for off-label prescribing?

**JD** Off-label drug utilization is essential in oncology, when based on evidence. Specifically, there are several

cases in which off-label prescribing is recommended. For example, special patient populations, such as children and pregnant women, are usually not included on the label because substantial evidence of safety and efficacy has not been submitted to the FDA. Rare tumors are another example, as it is not feasible to obtain definitive evidence because clinical trials are not able to enroll a large number of patients. Also, to obtain FDA labeling for a specific drug in a specific condition, the manufacturer has to apply for it. Sometimes, the drug is already widely adopted in practice and there are no financial incentives to apply for FDA labeling for that indication. For example, cisplatin is only FDA approved for metastatic testicular, ovarian, and advanced bladder cancers, but is used in an off-label and evidence-based way for several other malignancies.

However, a particular drug that is considered effective based solely on biologic plausibility and is not supported by clinical trial data, when prescribed in an off-label way, has the potential to become a safety issue. This happens, for example, when one assumes that an active drug in advanced disease will be effective in the adjuvant setting. These hypotheses should be tested in clinical trials and not in an off-label manner. For example, consider bevacizumab (Avastin, Genentech), initially FDA-approved for stage IV colorectal cancer in 2004. In 2007, medical oncologists were surveyed regarding their treatment patterns for stage III colon cancer. Eleven percent of providers stated they would prescribe off-label bevacizumab for their patients. Additionally, 27% of these same providers would choose to receive the drug themselves, if they were the patients. This represented an extrapolation from the metastatic setting to the off-label adjuvant setting without supporting evidence. A subsequent phase III clinical trial has shown that bevacizumab does not offer any benefit in the adjuvant setting. Thus, patients received the drug without supporting evidence and, as a result, aside from toxicity, it was at best an expensive placebo without clinical value.

### H&O What are the possible benefits of off-evidence drug utilization? What are the downsides?

**JD** Clearly, there is no benefit or clinical value to patients if off-evidence drug use is ineffective or has no evidence of efficacy in clinical trials. Although there are very few studies that assess the use of off-evidence drugs in oncology, we believe off-evidence drug use is more common in the palliative setting, where the benefit would be to provide hope to the patient and family members. In addition to the financial implications, such as out-of-pocket costs, the patient may also experience toxicity from the

drug and decreased quality of life, without improvement in survival. From a research standpoint, reimbursement for an off-evidence drug outside of a clinical trial decreases the impetus to enroll the patient in a study assessing that agent for that indication. We believe that with the right information, incentives, and alternative options, there are more effective ways of supporting these patients. These alternatives would include a shift to palliative and end-of-life care or enrollment in a clinical trial.

### H&O What are the financial implications of off-evidence drug use?

**JD** Off-evidence drug use may lead to a patient receiving an expensive therapy with no objective clinical benefit, while experiencing toxicities (ie, a therapy with zero clinical value). The antineoplastic agents, supportive medications, and toxicities add to the cost of therapy. Costs to the individual patient may be in the form of copayment or out-of-pocket expenses. The financial burden of off-evidence drug use is also increased for payers who bear the remainder of the cost. These costs are eventually shifted to all the members of the insurance group that individual patient is a member of, and will be reflected in the form of increasing premiums. In the case of Medicare, the cost is ultimately shifted to tax payers. We are currently assessing claims for a large insurance company for treatment regimens in the setting of metastatic colon cancer that have recommendations against their use by practice guidelines.

### H&O What are the ethical considerations with off-label drug use?

**JD** A physician may experience fewer moral issues with the idea of prescribing off-label drugs when there is evidence to support their use. For example, when we see patients with cancers for which there is no specific treatment, often we have to tell them that there is no FDA-approved treatment for their disease. However, in some cases, we may be able to tell patients that there is limited evidence from early-phase clinical trials that a drug may provide benefit; or that the manufacturer is currently applying to obtain FDA approval for that indication. In these cases, the clinician takes on an additional responsibility by prescribing a drug that the regulatory body has not stated is safe and effective. However, the clinician would be doing so because he or she believes it is an appropriate option for a particular patient based on the available evidence. The worst case scenario is when patients are prescribed off-evidence therapies when alternative options exist, but the oncologist was either not aware of or not willing to consider these alternatives.

## H&O Have there been any government reforms in regard to off-label drug use?

**JD** The Omnibus Budget Reconciliation Act of 1993 mandated that Medicare provide coverage for off-label cancer drugs if they are supported by designated compendia. The secretary of Health and Human Services could also designate additional compendia references for coverage of off-label uses of cancer drugs as deemed necessary. Several years earlier, the Omnibus Budget Reconciliation Act of 1990 was passed, which provided similar provisions for Medicaid recipients (applicable to all outpatient oral and intravenous drugs). By 2008, 2 of the 3 initial compendia were no longer published, and 3 additional compendia were added (DrugDex, Clinical Pharmacology, American Hospital Formulary Services, and National Comprehensive Cancer Network), with more peer-reviewed journals included as references. The act also instituted an annual review, during which the Centers for Medicare and Medicaid Services would revise its choice of compendia every year. In theory, these compendia serve as a bridge between off-label usage and FDA-approved indications. Similarly, most private and commercial payers are required by relevant state legislation to cover off-label use of certain types of drugs, also based on compendia. Most recently, the FDA has also issued a guidance that permits drug makers to provide physicians with scientific articles of off-label drugs, with the condition that the journal is peer reviewed and has a disclosure policy. This would potentially improve information on evidence-based use of off-label drugs in oncology.

## H&O How can the FDA, the medical community, and the public come together to improve the quality of off-label prescribing?

**JD** There are 4 steps for the FDA, medical community, payers, and patients to take to ensure that off-label use of drugs in oncology is ethical and effective: obtaining and disseminating evidence, learning from limited evidence,

promoting evidence-based medicine while discouraging the use of drugs without evidence, and offering alternatives to patients and providers. Obtaining and disseminating evidence consist of promoting comparative effectiveness research and identifying the required level of evidence and clinical endpoints for different diseases. Making this information available to the medical community in a fast, easily accessible, and accurate fashion is key. The second step is to develop a system to effectively learn from off-label utilization in oncology. If a particular drug has limited evidence but is widely used outside a clinical trial, registries or prospective ways of assessing the outcomes of patients receiving these therapies should be developed. The third way is to provide incentives for high value-based care. In other words, to incentivize patients, payers, and providers to accept and follow evidence-based recommendations, while also developing reimbursement methods to deter the use of off-evidence therapies or low-value care. Finally, there need to be alternatives for practitioners and patients if no proven therapy or no evidence for off-label therapy are available. These alternatives may consist of encouraging end-of-life care discussions or a clinical trial referral, where patients will be informed of the drugs they are receiving, sign a consent form, and be evaluated for toxicities and responses in a systematic way.

## Suggested Readings

U.S. Department of Health & Human Services. Centers for Medicare and Medicaid Services. [https://www.cms.gov/CoverageGenInfo/02\\_compendia.asp](https://www.cms.gov/CoverageGenInfo/02_compendia.asp).

Van Allen EM, Miyake T, Gunn N, et al. Off-label use of rituximab in a multipayer insurance system. *J Oncol Pract*. 2011;7:276-279.

American Society of Clinical Oncology. Reimbursement for cancer treatment: coverage of off-label drug indications. *J Clin Oncol*. 2006;24:3206-3208.

Leveque D. Off-label use of anticancer drugs. *Lancet Oncol*. 2008;9:1102-1107.

Casali PG, Executive Committee of ESMO. The off-label use of drugs in oncology: a position paper by the European Society for Medical Oncology (ESMO). *Ann Oncol*. 2007;18:1923-1925.

Love N, Meropol NJ, Ravdin PM, et al. Which adjuvant systemic treatments (AdjRx) would medical oncologists (MOs) wish to receive if they had colon cancer (CCa)? A survey of 150 physicians. *J Clin Oncol* (ASCO Annual Meeting Abstracts). 2008;26:4049.