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EDITORIAL

Off-Label Use of Cancer Drugs: A Benchmark Is Established

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Off-label prescribing, which is broadly defined as the prescribing of drugs outside of the marketing authorization determined by a licensing body such as the US Food and Drug Administration, is a controversial issue. On the pro side, off-label prescribing allows individual clinicians to make the ultimate decision as to whether or not a particular licensed drug is of potential benefit to an individual patient. There are a number of circumstances in which a physician may be compelled to prescribe off label, some of which may be considered more appropriate than others. Early use of an already licensed drug in a setting that is supported by data from a newly reported randomized study, but that has not yet been vetted through the drug approval process, may be an example of a more appropriate off-label use. This may be particularly salient when the approval process is slow, thus limiting access of patients and providers to effective treatments in a timely manner. Additionally, for many cancers, notably rare tumors, there may never be enough evidence to support a labeling indication because of the inability to conduct the appropriate trial as a result of inadequate patient numbers or lack of financial incentives. Not surprisingly, a previous survey found that American oncologists do discuss off-label use with their patients and feel comfortable prescribing for off-label indications in some circumstances.[1]

On the con side, the main criticism of off-label prescribing has been the concern that it jeopardizes patient safety because the full risk-benefit ratio is often not completely understood in circumstances where off-label prescribing occurs. Furthermore, by potentially reducing the availability of patients for clinical trials,[2] off-label prescribing may compromise our ability to obtain the high-level evidence that is needed to inform the risk-benefit calculations and support additional marketing authorizations by regulatory agencies. Even when approvals are obtained, the risk information may be inadequate; at present, the mechanisms for postmarketing monitoring of drug toxicity are far from ideal.[3]

In general medicine, the prevalence of off-label prescribing has been estimated to be approximately 20%.[4] There are a number of unique aspects of off-label prescribing in cancer, such as the need for timely treatment coupled with the toxicity and cost of many cancer drugs, which may impact the frequency and acceptability of off-label prescribing and underscore the need for cancer-specific research. Unfortunately, there have only been a handful of studies in oncology (predominantly, single-agent studies) that have evaluated off-label use.[5,6]

In the article that accompanies this editorial, Conti et al[7] report one of the most comprehensive studies of the current extent and cost of off-label prescribing of expensive cancer drugs in the United States. The authors evaluated the prevalence and associated cost of off-label prescribing of 10 patent-protected, commonly prescribed cancer drugs in 2010 using prescribing data from a large, nationally representative pharmacy database. They found that approximately 70% of claims were on label. Among the 30% of claims considered to be off label on the basis of the US Food and Drug Administration–approved indication, 14% conformed to National Comprehensive Cancer Network (NCCN) –supported off-label indications, and 10% of off-label use was in the same cancer site but not the stage or line of therapy as that stated on the US Food and Drug Administration label. The annual cost of off-label use was approximately $4.5 billion. The prevalence of off-label use varied significantly by drug; agents such as bortezomib and trastuzumab were generally used on label, whereas other drugs, especially rituximab, gemcitabine, and bevacizumab, were more commonly used off than on label. In fact, off-label use of bevacizumab was the single largest contributor to the cost of off-label prescribing.

The study[7] is a welcome addition to the evolving literature on off-label prescribing in oncology, given that it provides us with the most comprehensive, to-date, contemporaneous snapshot of off-label prescribing in the United States. Because not all off-label prescribing is bad, the authors should be commended for their efforts to dig deeper into off-label prescribing by categorizing each individual off-label use into that conforming to the NCCN compendium or at least cancer site, given that it provides us with a more complete picture about the extent of potential inappropriate prescribing. However, there are limitations with this further breakdown that merit discussion. A recent systematic review[8] of several drug compendia used for reimbursement decisions found that many compendia were out of date and lacked methodologic rigor and transparency in their review process. Furthermore, a drug that may have a favorable risk-benefit profile in one setting in a specific cancer may not have the same risk-benefit profile in another setting in the same disease. For example, in colorectal cancer, several agents (including bevacizumab) that have been proven to be of benefit in the metastatic setting have failed to improve outcomes in

the adjuvant setting.[9] Despite this lack of demonstrated benefit, bevacizumab is still being used by some oncologists in the adjuvant setting.[5,10] Bevacizumab was recommended in this setting in the 2010 version of the NCCN compendia (which was used as a reference for appropriate use in the study by Conti et al[7]), at which time point there was no evidence to support its use in the adjuvant setting outside of clinical trials, and the negative National Surgical Adjuvant Breast and Bowel Project (NSABP) C-08 adjuvant study[9] had already been presented at the 2009 American Society of Clinical Oncology annual meeting plenary session. These observations showcase the limitations of compendia updating at a practical level and they underscore the failure to change a recommendation in a timely fashion.

The focus on intravenous anticancer agents by Conti et al[7] does not address one of the greatest gaps in knowledge in this area, that is, use of the increasing number of oral anticancer agents, many of which are also extremely expensive and toxic. In terms of generalizability, the sample is nationally representative geographically but is limited predominantly to private practice settings, and a previous survey suggested that academic oncologists may be more likely to prescribe off label than nonacademic oncologists.[1]

Despite the above limitations, the work by Conti et al[7] contributes to the debate on off-label prescribing by providing us with a benchmark to begin the discourse on off-label prescribing in routine practice in oncology. Should we worry about their findings? My opinion is that for certain drugs, the answer is yes. The overall proportion of off-label use that the authors identified is not high, especially when taking into account NCCN-approved indications, but the variation by drug and the associated cost are high. The ultimate goal should not be zero off-label prescribing, but rather that the entire system be designed to maximize the likelihood of an optimal risk-benefit ratio for both individual patients and the system as a whole. It is unrealistic to expect that each individual case of off-label use would undergo the level of scrutiny that a marketing authorization would, nor will every treatment decision adhere exactly to a scenario that was addressed in the trials that led to labeled indications. It is also neither necessary nor desirable that rigid limits be placed on what can or cannot be prescribed in every clinical situation. What is needed is a framework that works across settings, from drug approval to reimbursement to individual patient decision making, to ensure that off-label prescribing, when it does occur, balances timely access to effective treatment with patient safety.

At the drug approval level, a number of solutions to the issue of off-label prescribing have been proposed, including reforms in the process used to approve (and develop indications for) drugs, as well as the use of novel approval mechanisms such as "coverage with evidence in development."[11(p61)] A number of jurisdictions, including the United States and, more recently, France[12] and Ontario, Canada,[13] have implemented procedures to gain additional information on drugs in settings where there is mounting information but insufficient evidence for a full approval. However, in the short term, the greatest opportunity to optimize off-label prescribing is likely at the reimbursement level. The use of ancillary tools such as drug compendia to make coverage decisions has generally been viewed as a good solution but, as noted, there are concerns regarding the quality of such compendia. On the part of payers, there should be greater scrutiny of reimbursement for drugs that are potentially toxic and expensive and are associated with a high proportion of off-label prescribing. In my view, any of the agents in the study by Conti et al[7] for which greater than 50% of use is off label meet those criteria. However, there will always be situations in which neither innovative coverage nor reimbursement mechanisms will be applicable. In these instances, a thoughtful evaluation of the available information coupled with an open discussion of potential risks and benefits between the physician and the patient will be necessary. In some circumstances, a form of peer review[14] could be used to evaluate situations in which off-label prescribing does not conform to compendia use.

In summary, the study by Conti et al[7] sets a benchmark for discourse on off-label prescribing in routine practice in oncology. Although their overall estimation is reassuring, their findings on individual agents, especially those for which more than 50% of use is off label, are of concern. There is a need for additional information, especially on the extent of off-label prescribing of oral cancer agents. In the meantime, investment is needed to facilitate the process of drug prescribing in oncology at the patient, provider, and system levels to warrant that the prescribing that does occur ensures the optimal risk-benefit ratio for individual patients and the system as a whole. Greater scrutiny at the reimbursement level is most likely to have the greatest impact in the short term.

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