Off-Label

John V. Cox, DO, MBA, FACP

What is old, is new again. Off-label use of oncology drugs is common and has long been the focus of controversy. Payers are often confused by the broad use of a therapeutic agent across seemingly unrelated diagnoses. They look to the FDA label for guidance on the specific use of a drug, yet these indications are often narrow and outdated. After the loss of patent protection, few companies invest in the costs to present evidence for a new label indication for a drug. An example is *cis*-platin, which is labeled for use in metastatic testicular, metastatic ovarian, and advanced bladder cancers. This labeling clearly does not reflect the current usage of this drug.

In the late 1980s and early 1990s, the off-label issue motivated oncologists to fight for regulatory and legislative relief. Many state oncology societies were organized to press state insurance boards and legislatures to mandate rational mechanisms of reimbursement for off-label oncology drugs. In 1993, Senators Rockefeller and Levin penned eponymous legislation that outlines methodology for Centers for Medicare and Medicaid Services (CMS) coverage for off-label oncology drugs. That mechanism defined three pathways for off-label coverage.¹ By far the most widely used are the compendia listings that practices use daily to justify the use of drugs for specific diagnoses. The legislation originally detailed three specific compendia; however, in 2008 CMS updated the compendia system and created a process for evaluating current and new compendia.² There are now four approved compendia in use (DrugDex, Clinical Pharmacology, AHFS, and National Comprehensive Cancer Network). If an off-label indication is listed in any of the compendia as being supported at a given level of evidence—and is not defined by any one of the compendia as being useless—then that indication should be covered. The legislation also allowed coverage for indications supported by studies in a list of select peer-reviewed journals (recently updated by CMS³), as well as for those considered “generally safe and effective.” These same processes have largely been adopted by private carriers, and over the past decades oncology patients have generally been able to get their treatments under these mechanisms.

But times do change. For many reasons, including oncology drugs' share of health care costs, scrutiny over the use of oncology drugs is rampant. Compounding the scrutiny by insurers and regulators is public and legislative scrutiny of FDA approval processes, which has focused mainly on postapproval safety concerns. Narrowing of approval language to specific, evidence-based indications is clearly the order of the day. Added to these issues are the upcoming changes in practice infrastructure. Adoption of electronic health records and the upcoming transition to ICD-10 will allow for more accurate diagnosis coding on claims than the current ICD-9 codification. The complexity of off-label drug use in oncology will be redefined by all of these parameters and more.

Through the seemingly narrow portal of the off-label coverage concerns, one confronts the issue of quantifying the value of individual

therapies. At heart, whether for the patient, the payer, or the regulator, the issue of whether a given treatment should be covered for a given diagnosis is one of value. This demands more information and research. Oncologists must help define the constructs of these arguments so that our patients can benefit from the therapies available.

I was prompted to reflect on this topic by the article by Van Allen et al in this issue of *JOP*. They illustrate many of these issues related to off-label use by looking at the use of rituximab. Their data are drawn from a large multipayer insurance database. One can imagine that similar analyses are ongoing by individual payers and regulators.

Other topics addressed in this issue include the evaluation of tools to assess clinical trial complexity and workload capacity in oncology clinical trials. The article by Smuck et al outlines a structured approach for this assessment, providing practices with a means of anticipating the complexity of a given trial and planning for the resources necessary for participation. A related subject is dealt with by Baer et al in the ongoing series highlighting exemplary practices of research. The authors remind us of the depth of responsibilities undertaken by signing form FDA 1572, which outlines the formal roles of an investigator overseeing a clinical trial.

Practices will gain information from three articles herein. Gesme and Wiseman add to their ongoing series detailing aspects necessary to career success. They provide wise advice to practices in their piece regarding performance appraisals. Large companies have long had formal, structured assessments of employees. Oncology practices need to take note of their advice to regularly assess and guide the people that make up the practice (including the physicians). Insights into survivorship programs and copay assistance for oncology patients are also presented in articles by Hahn et al and Rajurkar et al, respectively.

ASCO recently readdressed the former bisphosphonate guideline. In this issue, a summary of the new bone-modifying agent guideline is presented, as along with a thought-provoking commentary on the guideline by former ASCO president Gabriel Hortabagyi.

It is our hope that one or more of the articles in this issue will prompt your own reflections. The Editors would love to hear from you. Whether you have comment on any of the original contributions to the journal or suggestions on topics to be covered, we encourage you to write, and as always, we wish you good reading.

Accepted for publication on January 18, 2011.

DOI: 10.1200/JOP.2011.000220

References

1. Soares M: “Off-label” indications for oncology drug use and DrugCompendia: History and current status. *J Oncol Pract* 1:102-105, 2005
2. US Department of Health and Human Services, Center for Medicare and Medicaid Services: Medicare Coverage, General Information: Compendia 1861 (t)(2)—Anti-Cancer. www.cms.gov/CoverageGenInfo/02_compendia.asp
3. Recent developments in Medicare coverage of off-label cancer therapies. *J Oncol Pract* 5:18-20, 2009