Off-Label Use of Oncology Drugs: Too Much, Too Little, or Just Right?

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Off-label use of medications is a widespread occurrence in the United States health care system. The practice stems in part from narrow approval indications, crafted to optimize the chance of success for the treatment, and also from enthusiastic clinicians and manufacturers and confirming data that are often suggestive if not definitive.

The prevalence of off-label drug use is not well established and probably varies widely among specialties and drug categories. One widely cited study suggests that 20% of all office prescriptions are off-label.1 However, this analysis was based on primary care prescriptions. Among cardiac medications, antiseizure medications, and pain or sedative medications such as gabapentin or amitriptyline, off-label use accounted for between 45% and 80% of all prescriptions.

Given the study’s focus on outpatient, primary care medications, the findings have been considered less germane to oncology practices, in which many treatments are given by intravenous infusion for specific purposes. Off-label use among oncology drugs is not well characterized but is widely blamed for the expense of cancer care. Cancer drugs—especially newer ones—are costly. Some experts have argued that the fee-for-service payment system creates dramatic incentives for oncologists to prescribe new, expensive drugs, often in circumstances without “rigorous quality monitoring” for appropriate use.2 By implication, off-label use could be a “cost driver” in oncology.

But is it? For the first time, we now have estimates of the prevalence and cost of off-label use of expensive oncology drugs, and the results of this study do not suggest that minimizing off-label use will substantially alter the cost of cancer care.3 In this study, using pharmacy databases that track outpatient chemotherapy administration, investigators characterized use of 10 patent-protected, intravenous therapies as “on-label,” “off-label,” or, if off-label, conforming to the NCCN Drugs & Biologics Compendium (NCCN Compendium) or not. These particular drugs were selected because they are the kind often suggested as expensive newer drugs. Thus, the economic consequences of off-label use might be most profound with them.

The distinction between off-label and off-label but NCCN concordant is also a critical selection factor. The NCCN Compendium often endorses cancer treatments that are different from those strictly defined in an FDA-approval indication. However, as NCCN Compendium listings are drawn from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines), a compendium listing is recognized as valid and appropriate use, and this use is covered by CMS and most large private insurers. Thus, both the NCCN Compendium listing and “on-label” use would constitute what most observers would consider appropriate use.

The 10 drugs in this analysis (albumin-bound paclitaxel, azacytidine, bevacizumab, bortezomib, cetuximab, docetaxel, gemcitabine, pemetrexed, rituximab, and trastuzumab) are products well-known to oncologists. The list includes 6 of the top 10 best-selling oncology drugs in the United States (compare the list at http://www.physiciansmoneydigest.com/practice-management/10-Best-Selling-Cancer-Drugs). So, do we use them as we are supposed to?

The answer, perhaps surprisingly, is yes. Seventy percent of estimated use was on-label. Of the remaining 30%, half was in accordance with the NCCN Compendium. Thus, only 15%, or less than one-sixth of use is outside standard recommendations. The percentage of use that was on-label was heterogenous according to the specific drugs. More than 50% of gemcitabine, bevacizumab, and rituximab use was off-label,

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though again, substantial fractions of that use were concordant with compendium recommendations.

In dollar terms, annual sales of these 10 drugs totalled $11.9 billion. Based on the percentage of indicated uses, $2.4 billion, or 20% of sales, would be neither on-label nor NCCN Compendium concordant. That number, although not inconsequential, was driven principally by use of rituximab and bevacizumab. This $2.4 billion estimate also probably overstates the real price of off-label use. Because off-label use is likely to be less effective and thus of shorter duration than on-label use, the number of treatment starts for off-label uses is likely to exceed the dollar volume of sales for off-label purposes.

What lessons can be drawn from this analysis of off-label oncology drug use and how are those lessons relevant to the national debate on improving cancer care and lowering the costs of treatment? First, it is encouraging that the vast majority of drug use is on-target, if not on-label. Most quality interventions aim for the Pareto principle 80/20 compliance rate, and in this study, 85% of drug use was either on-label or within accepted norms. The corollary is that over-worrying about off-label use of new oncology drugs would not bring much saving.

Many cancer centers have or are seeking pay-for-performance contracts designed to limit inappropriate use of expensive new drugs in cancer medicine. However, barriers to inappropriate use already exist, including the scientific literature, which guides clinicians and guidelines-makers toward recommendations, and the ability of third-party payers to deny claims for inappropriate use. That combination of “carrot and stick” seems to work quite effectively, and elaborate programs to further insist on compliance are not likely to bear major cost-saving fruit. Policymakers who seek to control the price of oncology drug services will need to look to other causes of expensive care, such as the actual price of the drugs, if they wish to curtail spending.

Not surprisingly, guideline-based care is at the center of this discussion. A potential criticism of high rates of compliance with the FDA indication or compendium-listed care is that compendia endorsements are too permissive. Nothing suggests that excessive permissiveness exists in the NCCN Guidelines, but the potential critique is a reminder that good guidelines make for good care. The evolving medical market is going to place increasing scrutiny on the quality and methodology of guidelines as it comes to increasingly demand adherence to those guideline standards.

References