Toward Patient-Centered Drug Development in Oncology

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As an oncologist, when I sit with patients to discuss starting a new chemotherapy regimen, their first questions are often “How will it make me feel?” and “How did patients like me feel with this treatment?” Regrettably, this information is generally missing from U.S. drug labels and from published reports of clinical trials — the two information sources most commonly available to people trying to understand the clinical effects of cancer drugs.

In 2011, 15 hematology–oncology drugs were approved by the U.S. Food and Drug Administration (FDA). In only one case — that of ruxolitinib for the management of myelofibrosis — was symptom information included in the portion of the label that manufacturers can legally use for marketing purposes. In fact, ruxolitinib was the first cancer therapeutic in more than a decade for which symptom information was included in a U.S. drug label.

Cancer-drug labels stand in sharp contrast to labels for other types of drugs, about 25% of which list the drugs’ effects on patients’ symptoms or functioning.\(^1\) That disparity is surprising, given how common symptoms and functional impairment are in patients with cancer and how toxic oncology drugs can be.

The FDA has taken several recent steps toward encouraging inclusion of the patient perspective in drug development. It issued highly influential guidance on the use of patient-reported outcomes (PROs) in drug development,\(^2\) collaborated with the Critical Path Institute and industry to form the PRO Consortium with the aim of developing robust symptom-measurement tools, and obtained support from Congress in the fifth reauthorization of the Prescription Drug User Fee Act (PDUFA) to expand its internal expertise on the methodology of measuring PROs. (Unfortunately, allocated PDUFA funds have been withheld, which substantially impairs the FDA’s ability to implement planned patient-centered programs.)

These FDA efforts are evident in the ruxolitinib label and in the label for abiraterone acetate, approved this year for metastatic prostate cancer, which describes beneficial delays in time to the development of pain and the need for opioid use. Yet in preapproval trials in patients with cancer, symptom or functional-status evaluations that meet the FDA’s standards remain rare.

Some experts have argued that the FDA has raised the methodologic bar too high, whereas others accuse the pharmaceutical industry of paying too little attention to patients’ experiences. The bottom line is that both regulators and industry continue to prioritize survival-based end points rather...
than patient-experience end points in cancer-drug development.

Yet as patients live longer with cancer, they must increasingly choose among agents with varying efficacy–toxicity balances. And as approved drugs continue to yield only tiny median survival benefits (often measured in weeks), patients understandably want to know how their peers felt during and after a treatment. Moreover, payers increasingly seek information about patients’ comparative experiences with different products, because patients with worse symptoms or functional status utilize more supportive services.3

On the industry side, information about the patient experience is sometimes gathered in preapproval “pivotal” clinical trials (trials intended to provide evidence of the safety and efficacy of a product to support regulatory approval) through questionnaires focused on health-related quality of life (HRQOL). Often, this information is gathered to satisfy European regulators as well as payers, who seek a demonstration of economic value. Unfortunately, these end points are generally exploratory, and protocol-specified hypotheses and analytic or statistical plans are lacking. Data are commonly missing, and the results are rarely (or

<table>
<thead>
<tr>
<th>Step</th>
<th>Responsible Party</th>
<th>Phase of Drug Development</th>
<th>Strategies</th>
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</thead>
<tbody>
<tr>
<td>1. Identify patient-centered outcomes (symptom, functional, and other outcomes affected by a disease or product and important to patients) through direct patient feedback</td>
<td>Drug developer</td>
<td>Before pivotal trials</td>
<td>Prioritize patient-centered outcomes planning at earliest stages of drug development; conduct literature review and qualitative research (focus groups, interviews), quantitative research (multisymptom screening questionnaire), or both; enable early collaboration between clinical development team and health outcomes experts</td>
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<td>2. Discuss plans for measuring and analyzing patient-centered outcomes at structured meetings between drug-development team and regulatory agency</td>
<td>Drug developer and regulatory agency</td>
<td>Throughout drug-development life cycle, starting during early-phase trials</td>
<td>Formalize meetings between developers and regulators discussing and prioritizing end points meaningful to patients with open communication, specific recommendations from regulators, collaborative selection of outcomes and measurement strategies, elucidation of relationships between patient-reported outcomes (PROs) and other end points</td>
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<td>3. Develop or select measures to evaluate outcomes using established qualitative and quantitative methods</td>
<td>Drug developer</td>
<td>Before pivotal trials</td>
<td>Complete before pivotal trial design to ensure appropriate selection of key and exploratory patient-centered end points, adequate understanding of how measures will perform, anticipated effect sizes, adherence to regulatory guidance</td>
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<td>4. Include PRO and other patient-centered measures in pivotal trials, with protocol-specified plans for statistical analysis as well as minimizing and handling missing data</td>
<td>Drug developer</td>
<td>Pivotal trials</td>
<td>Dedicate statistical power for analysis of selected key PRO end points with support from exploratory end points; use electronic data capture with backup data-collection strategies</td>
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<td>5. Engage patients representative of the target population</td>
<td>Drug developer and regulatory agency</td>
<td>Throughout drug-development life cycle</td>
<td>Use formalized approaches to obtain patient input on study inclusion criteria, outcomes, measures, end-point design, comparators, strategies for accruing and retaining participants, plans for dissemination and implementation</td>
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<td>6. Include PROs in drug labels to help patients and providers with decision making</td>
<td>Regulatory agency</td>
<td>Regulatory review</td>
<td>Create pathway for information about fatigue and health-related quality-of-life domains to be included in labels; facilitate qualification of existing PRO measures; consider measures of cross-cutting PROs that perform well in multiple subpopulations to be broadly acceptable without requiring further methodologic testing</td>
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highly selectively) included in primary publications of trial results and are generally not intended for inclusion in U.S. oncology-drug labels.

We can, and ought to, aim higher. The examples of ruxolitinib and abiraterone, as well as experiences outside oncology, demonstrate six key steps that can move drug development toward a more patient-centered approach—one in which developers and regulators systematically consider patient perspectives in the design, conduct, and reporting of research (see table).

In the case of ruxolitinib, the sponsor was a small company whose leadership was committed to including the patient perspective in key trial end points. When early clinical experience and published data for the target population revealed a constellation of symptoms related to the disease that were viewed as important by patients (step 1), the company began discussions with the FDA (step 2) and collaborated with academic researchers and a consulting firm to develop a patient-reported outcome measure (step 3). This measure was tested and refined through use with patients representing the target population before it was employed in a pivotal trial (step 4). The questions were loaded into a handheld device that patients used to report their own responses daily, with near perfect levels of compliance—despite their debilitating symptoms. The company had ongoing communication with and feedback from the FDA throughout this process.

Ruxolitinib demonstrates the particular value that PROs provide for understanding clinical benefits when studies are not designed to detect overall survival advantages and instead rely on end points such as tumor response, progression-free survival, or noninferiority. Although overall, ruxolitinib represents a success story, measurement of fatigue and HRQOL decrements—which are prevalent and widely viewed as important to patients—were not included as key end points because the FDA had methodologic concerns about them; these omissions resulted in a label containing an incomplete picture of the patient experience (steps 2 and 6 might have prevented this).

In the case of abiraterone, the company took a risk in its pivotal trial by expending statistical power to measure the time to opioid use among men with minimal baseline symptoms, when little was known about this end point in prostate cancer (step 4). It would also have been useful to include information about symptoms other than pain that are of interest to men with this disease; according to qualitative research conducted before the pivotal trial and formal patient-engagement activities, these would include symptoms such as tiredness or sleep disturbance (steps 1 and 5). Although a broad HRQOL tool was administered with positive results, there was no protocol-specified analysis plan for it, and it did not meet the FDA’s current methodologic threshold (steps 2 and 6).

For these key steps to be taken routinely, a fundamental shift in cultural orientation among drug developers and regulatory reviewers is imperative. Specifically, the patient experience of treatment with a given drug must be regarded as essential information about the properties of the product, without which our understanding of its risk–benefit profile is incomplete. This requirement applies equally to studies with end points based on survival (such as abiraterone) and those focused on tumor response (such as ruxolitinib).

Methodologic challenges exist but should not continue to be cited as insurmountable. They have been shown to be addressable in many trials, and multiple documents offering guidance on methods are available. Examples include minimizing and analyzing missing data, identifying meaningful score changes for questionnaires, and analyzing PRO data in nonblind-ed trials. Additional research is warranted both to advance measurement science in these areas and to develop measures in the public domain that meet regulatory standards.

But the principal barrier remains a failure to prioritize the identification and confrontation of these challenges up front. Moreover, when PRO measurement is left until the postmarketing phase, it is often too late to adequately measure outcomes in a comparative trial, which leaves the true effect of a product on the patient experience uncertain. Ideally, moving forward, whenever representatives of a pharmaceutical company and a regulatory agency sit down to discuss a product-development program, they will ask the same question my patients ask of me: “How does this product make people feel?”
Although health policy experts disagree on many issues, they largely agree on the shortcomings of fee-for-service payment. The inefficiency of a payment method that rewards increases in service volume, regardless of health benefit, has become practically indefensible. But replacing discrete payments for each service with bundled payment for a set of services does not simply promote efficiency; it also potentially promotes skimping on care or avoidance of costly patients.

The Center for Medicare and Medicaid Innovation at the Centers for Medicare and Medicaid Services recently announced a large-scale demonstration of bundled payments for hospital and post-acute care services, and President Barack Obama’s 2014 budget proposes to move forward with that approach. Lest we sacrifice quality and access in the pursuit of efficiency, it is worth considering whether a payment approach in which savings and risk are shared — a hybrid of a fee-for-service system and one providing rewards for spending reductions — will achieve a better balance of cost, quality, and access than a system of single bundled payments, at least until our capacity to measure patients’ care needs and outcomes is sufficiently robust.

The Medicare program already has considerable experience not only with capitation payments to health plans for the full range of Medicare services but also with bundled payments for sets of services: inpatient hospital services are bundled into “stays,” skilled-nursing-facility (SNF) services are bundled into “days,” and home-health-agency (HHA) services are bundled into “episodes.” That bundles’ powerful rewards for reducing costs create an efficiency–selection trade-off — simultaneously rewarding desirable and undesirable behavior — is old news. But even new news (regarding Medicare Advantage plans) documenting that technical payment refinements can reduce the rewards provided for avoiding costly patients or costly care also shows that behavior favoring service to low-cost patients over high-cost patients persists.

Experience with current prospective payments raises particular concerns about selection and skimping in post-acute care. The tip-off to the risk involved in offering powerful incentives for these providers to keep costs low is the presence of extremely high and varied profits, in a service area devoid of standards for high-quality care. In 2010, SNFs and HHAs earned profits of 19%, on average, and the top quarter earned in excess of 27%.

In theory, these high and widely varying profits might reflect variations in efficiency. But two factors other than relative efficiency probably explain these margins. First is that classification of patients into payment categories for rate-setting purposes is not sufficiently precise to eliminate variation in expected costs among the patients within a category — so providers serving patients whose care needs are lower than average for the category are overpaid, and those whose patients have above-average care needs are underpaid. Second is the long history of patient selection in nursing homes and recent evidence that the HHAs with the highest profit margins provide fewer visits, despite serving patients with greater measured care needs.

Given the weakness of patient classification and quality norms, policymakers would do well to heed previous advice that, in these circumstances, a hybrid approach better balances efficiency and appropriate care.