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Commentary

Thinking Systematically About the Off-Label Use of Cancer Drugs and Combinations for Patients Who Have Exhausted Proven Therapies

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Debates surrounding the appropriateness of expanded access programs and right-to-try laws center on the question of under what circumstances should cancer patients be able to receive drugs or combinations that have not fully completed the stages of drug development (not completed testing in phase I, II, or III). The commonality here is that the agent in question has not been approved for any use in the U.S. A path to the drug thus requires special logistics. However, the fundamental question raised by expanded access is a broader one. Given that many cancer drugs are approved for one indication but, once approved, can be used alone or in combination for many others, the core question of expanded access is: Under what circumstances should providers and patients be able to attempt drugs or combinations for indications for which we still lack formal clinical trials?

At the outset, let us stipulate that we consider this question only as it pertains to off-protocol use of these drugs (i.e., use outside of clinical trials) and for patients who have exhausted all proven therapies. When clinical trials are an option, we encourage their enrollment, and the ethics of such trials has been extensively discussed. But, outside of trials, few articles have tackled the off-protocol use of drugs for unapproved uses, although authors have recognized that this is a key challenge in clinical medicine [1] and such use is common. It must also be remembered that off-label use often pertains to cancer drugs with annual costs in excess of $100,000 [2]; thus financial implications of this use are large. As an example, one of us recently faced the question of whether, for a patient with relapsed refractory multiple myeloma, it was permissible to treat with daratumumab, a monoclonal antibody approved as single agent, in combination with pomalidomide—a combination that has demonstrated relative safety in phase I trials but lacks phase II or phase III efficacy results (i.e., no proof that the combination is better than either agent alone).

These kinds of questions are frequently encountered in clinical oncology, although reliable statistics are absent. For patients with relatively good performance status who are interested in pursuing more treatment but who have exhausted recommended options, many oncologists attempt single drugs or combinations that are not yet vetted.

We believe that a pragmatic framework can aid in such decisions. While we admit there is no canonical answer for what is best, we believe consideration of three factors may frame this topic. These factors are safety, efficacy, and cost, and are depicted in Figure 1.

Safety

It should be remembered that novel drugs and their combinations may have unexpected safety signals. For example, vemurafenib, a small molecule inhibitor of BRAF, and ipilimumab, an antibody against an immunologic checkpoint, are individually active in BRAF V600E mutant metastatic melanoma, but the combination demonstrated adverse hepatic toxicity in 66%–75% of patients when combined in a phase I study, requiring the trial to be halted [3]. Notably, this toxicity could not have been predicted, because the drugs have distinct (and non-interacting) mechanisms of action and non-overlapping toxicities. Thus, clinicians must consider that safety exists on a continuum, with drugs or combinations for which either no safety data exist (i.e., no phase I trials), phase I trial data exist and show relative safety at usual doses, or phase I trial data exist and confirm toxicity (e.g., the case of vemurafenib and ipilimumab). In all cases where phase I trial data demonstrate toxicity precluding further drug development, or are absent, we do not believe combinations should be attempted, irrespective of cost.

Efficacy

The majority of cancer drug approvals are based on a surrogate endpoint, which may or may not predict improved survival or quality of life—true, patient-centered efficacy endpoints. Moreover, just 8% of National Comprehensive Cancer Network guidelines are based on level I evidence [4]. For these reasons, it is incredibly common that oncologists have to make treatment recommendations for patients while lacking strong evidence that our choices either improve survival or quality of life [1] over placebo [2] or other available standards of care. In some cases, however, randomized trials may have been performed and the results may be positive or negative. In the latter case (well-done, negative randomized trials), we believe that insurers should not be asked to pay for refuted treatments. For example, societal payers should not pay for sorafenib in the adjuvant setting of hepatocellular cancer. In some cases of contradicted practices with severe toxicity, no

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Safety data	Efficacy data	Insurers should pay for the treatment combination (at today's high prices)	Insurers should pay for the treatment combination (if at moderate prices)	Patient should be allowed to use his/her own funds/resources to take the combination
None	None	No	No	No
Phase I shows safety concerns	None	No	No	No
Phase I shows relative safety	None	No	Maybe	Yes
Phase I shows relative safety	Phase II/III trial with negative results	No	No	Maybe*
Phase I shows relative safety	Phase II/III trial with positive results	Yes	Yes	Yes

Figure 1. Decision-making model for off-protocol use of the novel treatment combination of daratumumab and pomalidomide in clinical oncology. *, For compelling, but still hypothesis-generating, subgroups and relatively low toxicity interventions.

provider should offer the treatment regardless of patient desire or willingness to pay (e.g., autologous stem cell transplantation for breast cancer).

Cost

The cost of cancer drugs is a critical issue in cancer care. Cancer drugs cost more in 2016 than in any time in history, and analyses show the cost is not proportionate to novelty, basis of approval, or clinical benefit [2]. In defiance of all traditional market principles, the price of many cancer drugs, such as imatinib, has risen from approximately $30,000 per year to more than $100,000, as patent exclusivity has wound down and the number of competitors has grown [5, 6]. Furthermore, these high prices are for drugs that often offer simply marginal benefits and, thus, have extraordinarily high cost-effectiveness ratios. For instance, pertuzumab prescribed for metastatic breast cancer costs $700,000 per quality-adjusted life-year (QALY) [7] and regorafenib costs more than $900,000 per QALY [8]. Thus, any consideration of off-label use of cancer drugs cannot ignore the elephant in the room: cost.

The reality is cancer doctors have at least some obligation to society to consider the financial impact of care [9], and this is especially the case in situations where unproven care is attempted. We believe that a framework to consider the feasibility of a medical practice must include cost because whether something is worth pursuing differs based on whether insurers (society) incurs the bill or whether individual patients choose to use their own funds (patients, of course, have substantially more freedom to do what they want with their money). As an intermediate scenario (Fig. 1), we consider the possibility that the patient requests a medication that is priced moderately (e.g., an off-patent cytotoxic, or ketoconazole in prostate cancer).

Putting It All Together

At the outset, we concede that there is no single right answer when the off-label use of drugs is permissible, but Figure 1 captures how we think about the issue. In the figure, "Maybe" is used to signal dispute between the two authors of this piece, and likely others may wish to make other alterations.

We believe that unsafe drugs or combinations should not be attempted irrespective of theoretical efficacy or where the cost falls. We believe that safe combinations of varying levels of efficacy (untested, contradicted, or validated) can be attempted and covered but that the cost, and whether and to what degree society bears those costs, may provide additional guidance. In general, we favor patients' right to use their own money as they see fit; however, grossly unsafe practices should not be allowed. Nevertheless, we understand that others see it differently. We have spoken to academic oncologists who believe the answer to nearly all the boxes (except the last row in Figure 1) should be no or, alternatively, that we should be more permissive.

Our model provides guidance in the described situation of daratumumab and pomalidomide (phase I data show safety; no efficacy data). Given current prices, it should not be attempted, but if the drugs were priced modestly or patients were willing to incur the cost, it perhaps could be. Others may feel differently about any of the boxes in Figure 1, and we encourage others to formalize their thinking about off-protocol use of novel combinations in clinical oncology. This practice is widespread and in need of standardization.

Disclosures

The authors indicated no financial relationships.

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