Interventional Pharmacoeconomics: A Novel Mechanism for Unlocking Value

Anthony V. Serritella[1,†], Garth W. Strohbehn[1,2,†], Daniel A. Goldstein[2,3,4,5], Allen S. Lichter[2] and Mark J. Ratain[1,2,*]

Cancer care's sustainability is challenged by drug expenditures. In the absence of systemic change, innovation is needed to curtail drug costs. Interventional pharmacoeconomics (IVPE) utilizes clinical research to identify safe, efficacious, cost-conscious dosing regimens to extract maximum value from expensive therapies. Strategies include de-escalation of dosage, treatment duration and administration frequency, and substitution with therapeutic alternatives. In this review, we discuss how IVPE strategies have been successfully used and could be implemented going forward.

OPPORTUNITIES FOR VALUE IMPROVEMENT IN ONCOLOGY CARE

The costs of oncology drugs routinely exceed US $100,000 per patient-year of treatment, endangering patient access and adherence to cancer therapy, and threatening whole health systems.[1] Targeted therapies, such as monoclonal antibodies and oral small molecules, now comprise the bulk of anticancer drug expenditures, with newly developed oral drugs experiencing sustained price increases of > 10% annually.[1] This trend is not expected to change, especially because 35 new oral molecular entities received US Food and Drug Administration (FDA) approval from 2013 to 2018, with more new agents expected in the future.[2]

The understanding of cancer's mechanisms has progressed tremendously over the past 30 years, allowing for the development of precisely targeted therapies. Despite these revolutionary therapeutic improvements, the methodology of early-phase clinical trials has remained static. Intravenous cytotoxic chemotherapies often have a steep dose-response relationship and, as a result, early dose-finding studies have attempted to identify a maximally tolerated dose (MTD) for use in phase II and III studies. This MTD is rarely reconsidered after approval and labeling.[3] By contrast, today's targeted therapies bind to a specific molecule and often demonstrate limited to no efficacy beyond a certain dose, making the MTD concept much less relevant.[3,4] Many early phase studies of modern targeted therapies still continue to seek the MTD, and rely on this MTD for later phase trials and potential labeling.[3,4]

Re-evaluating dosing strategies represents an opportunity to achieve significant value for patients. Randomized dose-ranging phase IIb trials are a standard approach outside of oncology to evaluate dose-response relationships, optimize dosing practices, and better characterize drug pharmacokinetics.[4] Even though off-label prescribing is common in oncology, off-label prescribing with the goal of reducing costs is not often undertaken. Value-based prescribing strategies for oral oncology drugs alone could save US $12 billion or more globally per year.[5]

In this review, we discuss IVPE as a promising mechanism for achieving value-based prescribing. We draw on our collective experiences in oncology to offer potential strategies for IVPE study design. We close with thoughts on ways to collaboratively promote adoption of IVPE study outcomes.

INTERVENTIONAL PHARMACOECONOMICS—MECHANISM TO DISCOVER HIGHER VALUE

IVPE studies seek to develop evidence for off-label treatment regimens that maintain equivalent therapeutic efficacy but substantially reduce costs borne by patients and health systems.[6] Based on their pharmacology, many drugs are candidates for studies of dose, schedule, and/or duration (**Table 1**). Clinical pharmacologists could play a significant role in helping identify such opportunities. Moreover, therapeutic de-escalation can reduce avoidable patient toxicities. Rather than relying on legislative or regulatory action, IVPE leverages clinical research to achieve systemic cost reductions within the free market.[3] Savings could be passed on as lower insurance premiums or copayments.[7] This section discusses potential approaches to therapeutic de-escalation.

Lower dosages with comparable efficacy

As discussed above, many drugs are administered at dosages greater than necessary to achieve their therapeutic effect. For example, the oral Bruton tyrosine kinase inhibitor ibrutinib approved for hematologic malignancies, such as chronic lymphocytic leukemia (CLL), has a standard labeled dose of 420–560 mg per day, despite phase I data demonstrating 97% of Bruton tyrosine kinase inhibition was achieved at a lower dose of 2.5 mg/kg/day (or about 175 mg/day).[8] Stepwise reduction of ibrutinib dosing in patients with CLL from 420 mg/day (3 tablets) to 280 mg/day (2

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[1]Department of Medicine, The University of Chicago, Chicago, Illinois, USA; [2]Value in Cancer Care Consortium, Ann Arbor, Michigan, USA; [3]Tel Aviv University, Tel Aviv, Israel; [4]Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel; [5]Department of Health Policy and Management, Gillings School of Public Health, University of North Carolina, Chapel Hill, North Carolina, USA. *Correspondence: Mark J. Ratain (mjr1@uchicago.edu)

†Contributed equally to this work

Table 1 Summary of Drug Candidates for IVPE Interventions

Drug	Possible change(s)	Reference(s)
Lower dosage with comparable efficacy		
Ibrutinib	Reducing dose from 420 mg to 140 mg daily	8
Erlotinib	Reducing dose from 150 mg to 100 mg or 50 mg daily	5
Dasatinib	Reducing dose from 100 mg to 50 mg daily	5
Pembrolizumab	Converting from flat 200 mg dose to 2 mg/kg dose	10
Reduction in dose through leveraging food effect and drug-drug interactions		
Abiraterone	Converting from 1,000 mg fasting to 250 mg with food	11,14
Lapatinib	Converting from 1,250 mg fasting to 500 mg with food	16
Pazopanib	Converting from 800 mg fasting to 600 mg with food	12,17,18
Ceritinib	Converting from 750 mg fasting to 450 mg with food	19,20
Cobicistat	Cobicistat 150 mg with food to enhance pharmacokinetics of atazanavir (300 mg daily) or darunavir	25
Venetoclax	Converting from 400 or 600 mg to 70 mg daily when taken with posaconazole	29
Less frequent dosing with comparable efficacy		
Nivolumab	Every 8–12 week dosing	6,30
Atezolizumab	Every 8–12 week dosing	31
Pembrolizumab	Every 8–12 week dosing	6
Trastuzumab	Every 6 weeks or longer dosing	6
Pertuzumab	Every 6 week or longer dosing	6
Shorter duration of treatment with comparable efficacy		
Imatinib	Consideration of discontinuation if parameters met	32
Trastuzumab	6 months of adjuvant therapy	33
Nivolumab	Consideration of < 24 months duration of therapy	35,36
Atezolizumab	Consideration of < 24 months duration of therapy	35,36
Pembrolizumab	Consideration of < 24 months duration of therapy	35,36
Bevacizumab	In lieu of ranibizumab in age-related macular degeneration	38
Sirolimus	In lieu of everolimus in cancer-related indications	39,40
Biosimilars	In lieu of reference products	41

IVPE seeks to actively decrease prescribing costs through the development of new dosing regimens that maintain equivalent efficacy. There are several main IVPE strategies. The first strategy reduces the dose of some drugs (e.g., ibrutinib, erlotinib, and dasatinib) while providing equivalent therapeutic efficacy. Secondly, some drugs have an oral bioavailability that is significantly boosted by combination with food and either have been shown in the past (e.g., abiraterone) or could be shown in future studies to be dose reduced through combination with food. Pharmacokinetic enhancers (e.g., cobicistat) could be used in select situations to similarly boost oral bioavailability, especially when food combination or other IVPE strategies are not possible. Some drugs (such as nivolumab, atezolizumab, etc.) are candidates for reduction in frequency of dosing, while others (e.g., imatinib) are candidates for studies of shorter durations of treatment. Some drugs (such as bevacizumab and sirolimus) could be substituted for more expensive treatments at a fraction of the cost.
IVPE, interventional pharmacoeconomics.

tablets) to 140 mg/day (1 tablet) over three 28-day cycles maintained ibrutinib's therapeutic effect and reduced off-target effects on platelet function all while reducing ibrutinib-related expenditures by two-thirds or more.[8] Ibrutinib's cardiac toxicity, which can be fatal, further motivates study of lower dosages.[9]

Ibrutinib is not the only oral tyrosine kinase inhibitor (TKI) for which dose reduction without loss of efficacy may be possible. A recent study listed 19 drug candidates for dose reduction.[5] Erlotinib in non-small cell lung cancer or dasatinib in chronic myelogenous leukemia (CML) are compelling examples of small molecule inhibitors with equivalent efficacy below their maximally tolerated or labeled dose.[5] Full economic analyses of these opportunities have not yet been performed.

Monoclonal antibodies targeting programmed death-1, such as pembrolizumab, provide opportunities for dose reduction.

The current labeled dose for pembrolizumab is 200 mg every 3 weeks,[10] and yet several studies, including KEYNOTE 010, demonstrated similar response rates and toxicity profiles with 2 mg/kg and 10 mg/kg doses.[10] Utilizing the personalized 2 mg/kg dosing for an average American adult markedly lowers doses. For non-small cell lung cancer alone, lower dosing could conservatively reduce costs by ~ 25%, generating over US $800 million in annual savings.[10]

Reduction in dose through leveraging the food effect and drug-drug interactions

Food can have profound effects on oral drug bioavailability. Whereas drugs in other branches of medicine are typically labeled to be taken with meals when their absorption is increased by food,[11] oral oncology drugs have frequently been labeled to be

taken fasting despite large food effects that increase their bioavailability.[12] Taking advantage of this food effect could achieve dose and value optimization for these drugs.[13]

Abiraterone, an inhibitor of CYP17A indicated for prostate cancer, has a large food effect, potentially up to 10-fold with a high-fat meal.[11] Despite this well-described food effect, abiraterone is labeled to be dosed fasting.[14] A randomized, noninferiority study comparing abiraterone administered at 1,000 mg while fasting and 250 mg with a low-fat meal demonstrated noninferiority in clinical end points (such as prostate specific antigen (PSA) change) and pharmacodynamic effects (inhibition of androgen production).[14] Not only does lowering abiraterone's dose cut its cost,[14] but low-dose generic abiraterone has overlapping indications with other patent-protected prostate cancer drugs that have a 10-fold higher list price.[15]

Many TKIs have poor bioavailability that is increased with food. For example, dosing lapatinib with food could cut its dose by 60% or more, creating patient savings.[16] Similarly, agents, such as erlotinib, vemurafenib, nilotinib, and pazopanib, all have significant food effects, often near twofold or greater.[12,17,18]

Utilizing a drug's food effect may also mitigate adverse events. Ceritinib causes severe gastrointestinal adverse reactions in 95% of patients treated with a 750 mg fasting dose.[19] Thus, the FDA mandated a postmarketing study[19] of lower doses of ceritinib with food. Not only was a 450 mg dose better tolerated, but a lower dose with food still maintained therapeutic drug concentrations. This result led to an FDA label change[20] that would reduce per patient cost by 40%.[4]

As another example, the drug nilotinib (indicated for CML) has a significant positive food effect (especially with a high-fat meal) and carries a black box warning for QT prolongation and sudden death from food-induced overdose.[13] This black box also discloses the risk of food-induced sudden death, a warning not found in any other FDA-approved drug label. Thus, off-label dosing (i.e., a lower dose with food) would prevent the risk of food-induced sudden death and the occasional underdosing from an accidental fasting dose would be unlikely to significantly affect efficacy but would buffer against overdose.[13] A small pilot study demonstrated the feasibility of this approach.[21]

Arguments made against food labeling in cancer drugs include (i) unpredictable safety and efficacy due to variation in real-world dietary composition (e.g., fat content or meal size), and (ii) patients with cancer being too ill to consume consistent meals—both of which may lead to large variability in plasma drug concentrations.[22] However, in practice, medications with large food effects have *less* variable steady-state drug concentrations when taken with food as opposed to fasting.[12] Moreover, there is no evidence that patients with cancer diets vary any more than the diets of those taking medications labeled to be taken with food for other chronic conditions.[11] In fact, many of the patients who take TKIs are actually relatively asymptomatic and have regular oral intake for many years. Finally, unwarranted food restrictions might compromise the practicality of drug administration, resulting in decreased adherence.[13] At a population level, it may be easier for patients to take medications with meals rather than at specified times before or after a meal.

In certain circumstances, drugs can be co-administered with pharmacokinetic enhancers[23] to boost a desired drug's concentration and/or half-life. Pharmacokinetic enhancing strategies are commonly used in HIV therapeutics using either a low dose of the protease inhibitor ritonavir or the pharmacokinetic enhancer cobicistat[24] to potently inhibit CYP3A4 and increase systemic exposure of antiretroviral agents.[24] Cobicistat is the only drug that is approved specifically as a pharmacokinetic enhancer.[25] Ketoconazole, a CYP3A4 inhibitor, has been similarly combined with cyclosporine, tacrolimus, and sirolimus to decrease the cost of transplant rejection prophylaxis.[26–28] This type of strategy has had limited utilization in oncology. Venetoclax (used in many hematologic malignancies) can be dose-reduced by at least 75% when paired with posaconazole (a CYP3A4 inhibitor).[29] However, pharmacokinetic enhancers have not typically been used with oral oncology drugs to date.

Although pharmacokinetic enhancers improve the bioavailability of a desired drug, they carry considerable risks, such as inhibiting the metabolism of many concomitant medications. This could lead to undesirable and unpredictable off-target and second order drug-drug interactions, potentially resulting in serious adverse events. As a result, such strategies should be reserved for select situations in which costs are critically unaffordable and less risky IVPE strategies are not possible.

Less frequent dosing with comparable efficacy

Although oral drugs may be amenable to dose reduction, many injectable drugs are packaged in single dose vials. Therefore, dose reductions would not be expected to save costs because the same number of vials would need to be purchased. Alternatively, less frequent dosing could reduce costs, adverse events, and patient inconvenience.[6]

Nivolumab provides a useful example. Therapeutic activity and maximal receptor occupancy were found at dosages as low as 0.1 mg/kg every 2 weeks in a phase I trial, ~ 3% of the approved 3 mg/kg dose.[30] Recent *in silico* simulation studies found no meaningful safety or efficacy differences between the 3 mg/kg every 2 weeks schedule and 480 mg every 4 weeks, supporting an FDA label change to the latter schedule.[30] Even every 8–12 weeks or longer, dosing might maintain efficacy and may reduce costs by 50% or more.[6] Atezolizumab similarly meets its therapeutic trough concentration with less frequent dosing.[31] Pembrolizumab, trastuzumab, and pertuzumab are additional dose frequency reduction targets.[6]

Therapeutic drug monitoring (TDM) could guide the administration frequency of many oncology drugs. For example, under current dosing practices nivolumab and atezolizumab have trough concentrations that are likely well above their minimum targets. Although there are expenses associated with TDM, it could curtail long-run costs through more precise dosing.[30,31] Ideal candidates for TDM in the context of IVPE are expensive monoclonal antibodies that have a long half-life and significant interindividual and/or intraindividual variability in clearance.[30] TDM could, therefore, be used to determine when the next dose is appropriate, based on the goal of maintaining a therapeutic trough concentration. TDM could also theoretically improve the therapeutic index of these

drugs through de-escalated dosing by reducing the duration and frequency of adverse events, such as immune-related adverse events (irAEs) in checkpoints, inhibitors, and cardiomyopathy in anti-HER2-targeted monoclonal antibodies.[30] Finally, TDM could reduce medication preparation and administration costs, as well as those experienced directly by the patient, including travel to the infusion site, lodging, missed time from work, and copayments.

Shorter duration of treatment with comparable efficacy

Shorter courses of some treatments provide equivalent therapeutic effect with fewer adverse events and lower costs. This concept can be applied to oral TKIs, monoclonal antibodies, and chemotherapy. Early discontinuation of imatinib is feasible in patients with CML with undetectable BCR-ABL transcripts, with 50% of patients remaining therapy-free 24 months after discontinuation.[32] Equivalent efficacy and less cardiotoxicity are also observed in patients with early-stage breast cancer who receive 6 months of adjuvant trastuzumab instead of 12 months.[33] Similarly, 3 months of adjuvant chemotherapy is as effective as 6 months for certain patients with colon cancer.[34]

Checkpoint inhibitors are often administered for 2 years, despite no evidence to support that duration of treatment.[35] In contrast, many patients achieve their maximal response in shorter periods of time or have a durable response despite early discontinuation due to side effects.[36] Although many irAEs occur in a dose-dependent manner within 3–6 months of therapy, others occur years later.[37] Shorter checkpoint inhibitor duration could reduce the risk of irAEs as well as long-term toxicities not yet identified.[30]

Substitution of therapeutic alternatives with comparable efficacy

Less expensive alternatives of many drugs can be substituted without impacting efficacy. One encouraging ophthalmology example is the use of the vascular endothelial growth factor inhibitor bevacizumab in exudative age-related macular degeneration. A publicly funded randomized trial found off-label bevacizumab to be as efficacious as more expensive therapies that were specifically approved for age-related macular degeneration, leading to widespread bevacizumab adoption and Medicare savings of over US $17 billion.[38] Within oncology, newer and more expensive mammalian target of rapamycin inhibitors, such as everolimus, borrow heavily from the structure of sirolimus but differ little in terms of pharmacodynamic effects or tolerability. Substitution of everolimus with sirolimus[39] could reduce costs by as much as 89%.[40]

Biosimilars may exert downward pressure on established drug costs because they are expected to be 10–30% less expensive than reference products.[41] However, the adoption of biosimilars is fraught with challenges. Biosimilars, like reference products, are produced using living systems, are not bioidentical to existing drugs, and have production variability. IVPE optimization of existing drugs represents a larger and more immediate savings prospect, with biosimilars likely playing a complementary role.

CLINICAL TRIALS TO DEMONSTRATE VALUE

Once an IVPE opportunity is identified, a clinical trial is necessary to build evidence for the safety and preserved efficacy of the proposed practice. Even when an IVPE strategy is backed by strong pharmacokinetic and pharmacodynamic evidence, a clinical trial will best motivate off-label prescribing of a new practice.

A trial may also be useful to confirm a drug's pharmacokinetics using an alternative dose or schedule.[4] For example, the magnitude of a drug's food effect may ultimately be found to differ from that predicted by prior studies, as was the case for abiraterone.[14] A drug may also exhibit nonlinear pharmacokinetics, leading to a different food effect at de-escalated doses that were not previously studied.[16] Furthermore, the impact of food on chronic dosing or interpatient variability[16] may need better characterization. Finally, food's timing may influence drug absorption.[42] For lapatinib, such pharmacokinetic issues illustrated the need for a formal study before recommending off-label dosing.[16]

There may be disagreement over the appropriate end point for comparing the efficacy of existing dosing practices and de-escalated dosing. A drug's original registrational studies are likely to have been large, expensive, and measured long-term clinical end points. In contrast, IVPE studies will be smaller and use time-efficient end points to draw efficacy conclusions. Capturing biomarkers, pharmacokinetic, or pharmacodynamic end points may strengthen efficacy conclusions. For example, whereas a 12-week PSA change was criticized in the abiraterone study for not being a validated surrogate end point,[43] noninferiority in concomitant CYP17A inhibition alongside PSA progression-free survival bolstered the case for noninferiority in established outcomes like progression-free survival or overall survival. Metrics, such as tumor size or serum markers, like cytokine levels (as in ibrutinib's case)[8] could similarly be utilized. Clinical pharmacologists could then help address the inefficiencies in drug development identified by IVPE by incorporating more efficient practices in the future (especially early in development).

There also may be challenges in selecting the appropriate statistical method to compare trial arms. Classical noninferiority studies require large amounts of time and resources, yet still struggle to prove equivalency.[6] Furthermore, achieving consensus on the appropriate noninferiority margin is difficult.[43] Noninferiority margins could be tailored to a drug's cost, duration, or targeted condition to improve acceptance. A wider noninferiority margin may be acceptable for an expensive drug given for a long time, whereas a narrower margin may be appropriate for a less expensive drug given for a shorter time (such as for a curable condition). More efficient studies, such as Bayesian noninferiority designs[6] or *in silico* studies,[30] could be considered. IVPE trials could also be designed as superiority studies, aimed to reduce medical or financial toxicity.

FUNDING IVPE STUDIES

Funding for IVPE studies could come from entities that can extract significant value from study outcomes, such as payers.[7,10] In contrast to industry-sponsored studies, IVPE studies will be shorter term and smaller scale—likely trials of 300–400 patients—with data collection appropriate to address study aims, but not the scale required for potential regulatory approval.[44] Savings realized within a trial's de-escalation arm could fund a payer's trial expenses. For example, an ibrutinib trial where half of the patients are randomized to a reduced dosing arm could save ~ $85,000 per patient

enrolled over a 30-month time period. Even with trial costs as high as US $16,000 per patient, enrolling even 20 patients would fund the trial and still net almost US $1.4 million in savings over the same time period.[7] In the long term, a successful ibrutinib de-escalation trial could save payers billions of dollars annually.[7] This paradigm has been demonstrated in a payer-sponsored trial with interim results showing that reducing denosumab's dosing frequency by two-thirds decreased toxicity.[45]

Health systems that both fund and provide care are ideal settings for IVPE studies, effectively repurposing costs to fund studies.[7] These include government actors, such as the Veteran's Health Administration in the United States, the National Health Service in the United Kingdom, and nongovernment single payers, such as Kaiser-Permanente and Intermountain Healthcare in the United States, or Clalit in Israel.[7] Such systems could also easily implement a trial protocol. Self-funded corporations or government payers like Centers for Medicare and Medicaid Services (CMS) would similarly be incentivized to run such studies. Although challenging for a single private health insurer to conduct an IVPE trial,[7] a consortium of multiple insurers could provide funding, trial infrastructure, and a network for communicating results.[7]

Philanthropic organizations seeking to improve outcomes could contribute intellectual capital and valuable study experience to IVPE trials.[44] For example, the M.D. Anderson CLL Moonshot Program funded and provided significant expertise to the ibrutinib pilot trial.[8] Organizations such as the Value in Cancer Care Consortium[44] (founded by oncologists) also promote such studies.

PROMOTING ADOPTION OF TRIAL RESULTS
Although IVPE studies will be published in academic literature, they will not benefit from industry-funded studies' large marketing budgets. Therefore, additional efforts are required to promote IVPE study practices. Larger, long-term follow-up studies and post-study surveillance could build more evidence that de-escalatory practices continue to benefit patients.

Guidelines consortia can encourage the adoption of an IVPE practice as part of an orientation toward value-based care. In the example of abiraterone, despite some initial skepticism of the study,[43] groups quickly became more receptive. This was evident when some suggested low-dose abiraterone for a different prostate cancer indication.[46] Both the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines on prostate cancer[47] and an international guideline consensus report[48] endorsed lower dose abiraterone with food within 2 years of the trial's publication, further promoting the practice. Recognition of health system cost constraints should further encourage this practice.

Payers have an incentive to promote IVPE practices to physicians. Reimbursement could potentially be linked to practice adoption. Through a shared savings model,[49] financial incentives might be offered to physicians adopting high value prescribing practices. The oncology care model could pilot IVPE strategies using cost reduction and quality improvement targets to guide provider reimbursement. Similarly, a bundled payment system in which institutions receive a fixed dollar amount based on the standard costs of patient medications would incentivize lower cost (but equally efficacious) prescribing.[50]

Payers could also encourage patients to adopt IVPE recommendations. Payers already incentivize patients to undergo screening through discounts or reimbursements. Some payers even incentivize practices like filling prescriptions less expensively abroad.[51] An inclusive shared savings model could lower copayments or premiums to incentivize patients to be receptive to an IVPE recommended practice, such as taking a lower dose with food.[49] Higher dose and more costly regimens could be reserved for patients whose disease progresses through lower dose or lower cost regimens.

Prescribers and pharmacists could also collaborate to provide patients with detailed instructions for administering a drug less expensively within the context of a drug's pill formulations or packaging options. "Pack splitting" for the drugs lenvatinib and cabozatinib exemplify this approach. Using pharmacokinetic principles, alternative dispensing, and patient administration strategies would double the length of time patients could use existing drug blister packages.[52] These strategies preserved drug efficacy and decreased expenses by 50% (or as much as US $14,000 per patient-year).[52] Long-term counseling would enhance patient comfort with these tactics.

Although evidence for improved dosing strategies have led to label changes in the past (such as in the examples of ceritinib and nivolumab above), it is not the intent of IVPE to motivate label changes. Rather, IVPE's cost savings potential hinges on such changes *not* being adapted into the drug label. Given drug prices are not entirely a function of their production or development costs, it is likely more effective to generate evidence for off-label prescribing to disruptively bring down drug costs.

PHARMACEUTICAL OPPOSITION TO IVPE STUDIES
We anticipate pharmaceutical companies implementing strategies to make IVPE dosing challenging or less cost efficient. Strategies include raising prices or eliminating certain dosing formulations. A landmark study in the British Medical Journal (BMJ) demonstrated the problem of oversized vials.[53] It was estimated that $3 billion are wasted every year in the United States due to oversized vials. If attempts are made to reduce doses, the manufacturers could counter this simply by adjusting the vial sizes that are available. A classic example for this is the situation of pembrolizumab. Prior to the fixed dose of 200 mg every 3 weeks, pembrolizumab was dosed at 2 mg/kg every 3 weeks. At the time of weight-based dosing, the drug was available in both 100 mg and 50 mg vials. However, in line with the dosing change, the 50 mg vials were removed from the market, making it more difficult to use weight-based dosing.[10] However, even if attempts are made to perform vial sharing, there is no financial incentive for hospitals and clinics to provide lower doses, due to the existence of the JW modifier rule by the CMS.[54] This states that even if there is wasted drug in a vial, the cost of this can be reimbursed by the CMS. There would, therefore, be no financial incentive to make the substantial extra effort required to perform vial sharing.

A similar example can be seen in the setting of oral drugs. The You&i program[55] for ibrutinib aimed to remove the 140 mg capsule from the market, limiting dosing flexibility, while pricing newly introduced tablet formulations (140–560 mg) at 3 times the price

of the 140 mg capsule. Other strategies include paying physicians to prescribe on-label,[56] opposing experts who study dose de-escalation, or legal or regulatory action to discourage IVPE practices.

Such attempts may delay or interfere with implementation of IVPE practices, but, in some cases, have eventually failed. For example, drug makers eventually reversed ibrutinib's You&i program after public outrage.[55] The English High Court backed the NHS's off-label use of bevacizumab to reduce costs, despite manufacturer objections.[57]

CONCLUSION

Reducing drug expenditures is critical to ensuring the viability of all health systems. IVPE-based prescribing strategies represent an attractive path toward limiting prescribing costs and extracting value for patients. Although precise cost savings in the United States may be difficult to estimate, as they are a function of insurance plans and pharmacies, a preliminary analysis of all oral patent-protected oncology products suggested that an opportunity for at least 50% savings may exist for a large number of drugs.[5] Value-based prescribing strategies for oral oncology drugs alone could result in US $94,000 per patient-year in savings,[5] with a similar opportunity in long-lived parenteral monoclonal antibodies. Whereas this approach to drug use has been developed with a focus on oncology, the principles and practices described here could be utilized to bring down costs outside of oncology as well. Although optimal design and funding of IVPE studies are still debated and practice adoption is not without obstacle, this potential opportunity cannot be ignored.

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