MAYO CLINIC

The High Cost of Cancer Drugs and What We Can Do About It

Mustaqeem Siddiqui, MD, and S. Vincent Rajkumar, MD

Last year, ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY) was approved by the Food and Drug Administration (FDA) for the treatment of metastatic melanoma. The benefit in survival over and above standard treatment arms was 3.7 months in previously treated patients and 2.1 months in previously untreated patients.[1,2] The cost: $120,000 for 4 doses. As staggering a figure as that is, the drug is hardly alone in its lofty price. We believe that the immense cost of contemporary cancer drugs signals even greater costs for future drugs (Table).

In health care delivery systems in which third-party payers (private or government) cover the costs of cancer treatment and the insured public has a presumed and possibly legal right of access to all approved drugs, the soaring price of cancer drugs poses at least 3 major problems. First, the absolute cost to society will become increasingly unaffordable if every drug with statistically significant but clinically unimportant benefit is approved. Second, it becomes problematic for insurance companies to price policy premiums accurately[3] because the approval, clinical acceptance, and incorporation of expensive new drugs is unpredictable and geographically variable. As a result, insurance premiums need to be meaningfully increased to keep up with the cost of care. Third, almost all approved cancer drugs are eventually used for conditions and settings not approved by the FDA (ie, off-label use).[4,5] The data to support these indications are almost always much less rigorous than those used to gain FDA approval. Off-label use may increase expenditures on a drug that offers little or no efficacy.

For patients treated for cancer, the median out-of-pocket expenditure for patients with private insurance was approximately $1500 in 2003 to 2004, with 25% of patients spending slightly more than $5000. According to The Henry J. Kaiser Family Foundation, the median income (including social security, pensions, and other earnings) of Medicare beneficiaries is less than $22,000.[6] This fact raises serious questions as to how Medicare beneficiaries will be able to bear the increasing burden of health care costs. Indeed, the percentage of personal bankruptcies in the United States attributed to health care costs rose from 46.2% in 2001 to 69.1% in 2007.[7] More concerning, health care reform in Massachusetts (the template for national health care reform) did not seem to decrease the percentage of personal bankruptcies due to health care costs.[8] As serious as the problems are in the United States, there are additional issues in less wealthy countries, where resources are considerably constrained. With a much lower median income, the proportion of expenditures directly paid by the patient is much higher, in many cases approaching the entire cost. Physicians and patients in these countries look to the United States and the European Union for guidance on effective treatment options.

Although the rise in health care costs is multifactorial, many of us, particularly oncologists and hematologists, repeatedly ask ourselves the following questions: "Why are cancer drugs so expensive?" "What polices or interventions can be employed to lower the cost of cancer drugs?" The comments and perspectives herein are intended to stir debate and discussion. Our goal is to provide an overview of the major operant factors from a physician's perspective.

See editorial comment, page 932

From the Division of Hospital Internal Medicine (M.S.) and Division of Hematology (S.V.R.), Mayo Clinic, Rochester, MN.

Why Are Cancer Drugs So Expensive?

The high cost of cancer drugs is related to numerous factors. It is very expensive to move findings from bench to bedside and to perform all the regulatory studies (including phase 1, 2, and 3 clinical trials) to gain approval. Second, because most cancers are incurable, patients are treated with each approved agent (sequentially or in combination), creating a virtual monopoly because the use of one drug does not automatically mean that the others are no longer needed. Third, even when the monopoly is broken with the arrival of "new and improved" versions of an approved drug, the older (and by now generic) drug tends to be viewed as substandard treatment, thereby perpetuating the situation. Fourth, the very nature of cancer, and the seriousness of the diagnosis, plays a role in that patients and physicians are often willing to pay the high price of treatment even for marginal improvements in outcome. Finally, our systems provide an incentive to administer more chemotherapy, and there are legal barriers that prevent agencies such as the FDA from taking economic and cost-effectiveness considerations into account when approving new drugs.[9]

High Cost of Drug Development. Drug development costs are high. Many years and millions of dollars are spent in preclinical research to identify a compound or design a drug, describe its mechanism

TABLE. Cost of Selected Drugs Used in Cancer Therapy[a]

Generic drug name (trade name; manufacturer, location)	Cancer	Typical treatment schedule	Cumulative drug cost for 1 y ($)	Comments
Ipilimumab (Yervoy; Bristol-Myers Squibb, New York, NY)	Melanoma	Once every 3 wk for 4 doses	120,000	Duration not well defined; currently, physicians have been going past the 4 doses if patients have achieved a good response
Sipuleucel-T (Provenge; Dendreon Corp, Seattle, WA)	Prostate cancer	Three doses over 1 mo	90,000 for 3 doses	
Bevacizumab (Avastin; Genentech Inc, South San Francisco, CA)	Various cancers, including lung and colon cancer	Once every 3-4 wk	90,000	Can be continued >1 y until disease progression
Paclitaxel, protein-bound (Abraxane; Celgene Corp, Summit, NJ)	Breast cancer	Three times a month	80,000	Continued until disease progression
Lenalidomide (Revlimid; Celgene Corp)	Multiple myeloma	Daily for 3 wk of each month	90,000	In frontline and maintenance, duration of therapy can exceed 3 y; in relapsed disease, duration is approximately 1 y
Bortezomib (Velcade; Millennium Pharmaceuticals, Cambridge, MA)	Multiple myeloma	Once weekly	60,000	Can be continued >1 y until disease progression
Imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp, East Hanover, NJ)	Chronic myeloid leukemia	Once daily	70,000	Lifelong until progression
Alemtuzumab (Campath; Genzyme Corp, Cambridge, MA)	Chronic leukemias	Three times a week for 3 mo	70,000	Could be used for >1 y
Ofatumumab (Arzerra; GlaxoSmithKline, Philadelphia, PA)	Lymphomas and chronic lymphoid leukemias	Twelve doses over 3-4 mo	120,000	Could be used for >1 y
Brentuximab vedotin (Adcetris; Seattle Genetics Inc, Bothell, WA)	Hodgkin lymphoma	Once every 21 d for 8 cycles	100,000	Approximately 6-8 cycles in a year
Dasatinib (Sprycel; Bristol-Myers Squibb)	Chronic myeloid leukemia	Once daily	110,000	Lifelong until progression

[a] The costs listed are approximate estimates based on average wholesale prices and typical schedules used in practice. Costs are higher when the cost of administration is factored in and when 2 or more drugs are used in combination.

of action, and generate preclinical data. Pharmaceutical companies spent $50 billion in aggregate on research and development in 2008.[10] Once ready for clinical testing, the complexity of clinical research mandates careful administration of trials, large patient sample sizes, and long follow-up, all of which are expensive. Each drug is estimated to cost $1.2 billion to $1.3 billion in cash outlays per approved biopharmaceutical.[11] Although the patent life from date of filing is 20 years, the average time to bring an antineoplastic agent from the start of clinical testing to regulatory approval is approximately 8 years. This means that the actual patent life of a drug from the time of initial marketing can be limited, often less than 10 years. In addition, only 16% to 19% of products that enter clinical trials successfully make it to market on completion of the clinical testing and approval process.[10,12] To their credit, pharmaceutical companies are exploring ways to decrease drug development costs by using contract research organizations and contract manufacturing organizations. The retail prices of drugs are a function of the costs of development, the addressable patient population, the patent life, and the projected returns on investment.

"Monopoly." In our view, cancer drugs represent, for the most part, a monopoly. This is due in part to

Mayo Clin Proc. ■ October 2012;87(10):935-943 ■ http://dx.doi.org/10.1016/j.mayocp.2012.07.007
www.mayoclinicproceedings.org

the biological complexity of cancer and in part to the medical and regulatory system. It has been only 59 years since Watson and Crick described the structure of DNA. In the short period since, scientists have begun unlocking the secrets of mutagenesis, tumorigenesis, gene and protein expression, messenger systems, metastasis, and resistance to treatment. Although we have immensely increased our knowledge of cancer, there is still much more to learn. As such, most patients currently receiving chemotherapy will die of their disease. Because of this fact, there is no competition among truly effective cancer drugs to lower their cost. Let us examine this more closely.

In the case of most less-complex and curable conditions, pharmaceutical companies have been successful in developing multiple effective drugs. As there are many substitutes, competition among the pharmaceutical companies keeps prices reasonable. For example, there are many antibiotics to treat pneumonia, with a defined treatment duration. If a patient initiates therapy with one antibiotic and is cured, the patient will not need to use other antibiotics. Therefore, there is genuine competition among pharmaceutical companies to provide the most effective product with the least adverse effects at the best value. This is seldom the case in cancer therapy. *Mayo Clinic Proceedings* has published numerous articles highlighting the current treatment of cancer.[13-17] Most cancers are not curable, and most approved cancer drugs work only for a limited time. When one treatment fails, the patient will be treated with subsequent agents until all options are exhausted.[18] For example, let us consider that there are 4 approved drugs to treat a particular incurable malignancy. The availability of 4 options does not produce the necessary competition to keep prices down. Why? Because unlike the curable conditions discussed earlier, the choice of one drug does not preclude the concurrent or subsequent need for the other drugs. In fact, each drug is expected to be used in all patients during the course of their disease. Most of these drugs provide benefit for a short duration, typically measured in weeks or months, and then the tumor begins not to respond to the therapy. In this scenario, physicians really do not choose the most cost-effective option; they only decide the timing at which each option is used. Thus, each drug is an effective monopoly because each one will be indicated at some point during the course of a patient's illness. As in any monopoly, drugs that extend the survival of patients with incurable malignancies, even by a few weeks, can, therefore, be priced at whatever price the market will bear. Although the same situation may occur in other chronic incurable illnesses, the magnitude of the problem is amplified in malignancies because the impact and seriousness of a cancer diagnosis results in greater willingness on the part of patients and physicians to take on the high costs of treatment. This is evidenced by the elasticities (percentage change in use associated with a 1% increase in effective coinsurance rates) of specialty drug use by patients among 4 conditions: rheumatoid arthritis, kidney disease, multiple sclerosis, and cancer. For example, Goldman et al[19] reported that if an insurance plan were to double the cost of sharing for rheumatoid arthritis specialty drugs, overall spending on these drugs would decrease by 21%. However, for cancer drugs, spending would be decreased by only 1%. This is in contrast to traditional pharmaceuticals, where a 30% to 50% decrease in spending can be seen when copayments double.

Current legislation also contributes to the high cost of drugs in the United States. As written into the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Medicare is prohibited from directly negotiating with manufacturers. Negotiation, instead, is done through local contractors. In addition, an array of legislation prevents Medicare from categorizing cancer drugs with related chemical structures and indications from being considered interchangeable, thereby eliminating competition in the market for an indication. Therefore, every drug has its own payment rate and unique billing code. This prevents Medicare from using strategies such as blended reimbursement and least costly alternative, which it uses for noncancer drugs to decrease or control prices.[20] This cedes pricing power to manufacturers, thus making Medicare a price taker.

Lack of True Generic Price Check. One can argue that a monopoly as described previously herein would be temporary at best because eventually similar drugs of the same class would emerge, offering competition that should in theory act as a price check. However, owing to some of the factors described previously herein, the price check offered by generics in nonmalignant diseases[21-23] is effectively neutered in the case of cancer. For example, in nonmalignant diseases, a new and improved treatment that simply offers incremental benefits over established treatment but costs considerably more than the generic version will not be able to maintain a high price if the incremental benefits do not provide value to the patient. Patients and physicians will shift toward less costly, but nearly as effective, treatments. In the case of a life-threatening cancer, however, because the choice of the new medication is typically associated with metrics such as "superior responses," "improved progression-free survival," and "longer overall survival," the implications become more serious, and the older drug is rapidly

viewed as substandard treatment. Examples of this in cancer include thalidomide (Thalomid; Celgene Corp, Summit, NJ) vs the newer analogue, lenalidomide (Revlimid; Celgene Corp); imatinib mesylate (Gleevec; Novartis Pharmaceuticals Corp, East Hanover, NJ) vs nilotinib (Tasigna; Novartis Pharmaceuticals Corp); doxorubicin (Adriamycin; Bedford Laboratories, Bedford, OH, or Rubex; Bristol Myers Squibb, New York, NY) vs liposomal doxorubicin (Doxil; in the US, Caelyx; outside the US, Janssen Products, a unit of Johnson & Johnson, and Myocet; Enzon Pharmaceuticals Inc, Piscataway, NJ); and paclitaxel (Taxol; Bristol Myers Squibb Co, New York, NY) versus protein-bound paclitaxel (Abraxane; Celgene Corp). New versions of older cancer drugs do not become alternatives that engender true competition for price. Instead, these new versions over time become replacements for older medicines, sustaining the monopoly. The cheaper generic versions that survive in nonmalignant diseases through a variety of maneuvers become outdated and obsolete when it comes to cancer.

Seriousness of the Disease. Except for early-stage cancers, testicular cancer, and certain blood cancers, such as large cell lymphoma and childhood leukemia, most cancers are incurable. There are many things patients are willing to do without; however, medication for a fatal disease is not and should not be one of them. The seriousness of a cancer diagnosis plays a role in how much cost patients and physicians are willing to bear for modest incremental benefits. However, high prices for incremental benefits are a recipe for a system with unsustainable costs.

High Cost of Generic Cancer Drugs. Even if there are acceptable generic alternatives with equal efficacy, the prices of many such drugs for cancer are high compared with those for nonmalignant diseases. When imatinib (Gleevec; current cost, approximately $75,000-$100,000 per year) goes off patent, we forecast that it will likely be priced in the thousands of dollars per year. The price will reflect what the market will bear in general for cancer treatment and may factor in the relative cost of newer versions, such as nilotinib (Tasigna) and dasatinib (Sprycel; Bristol-Myers Squibb).[24] However, in our opinion, it will have little resemblance to the actual cost of manufacturing and distribution as there is simply no need to. At the same time, for older chemotherapy drugs, we recognize the need for balance: when generic cancer drugs are too inexpensive, and the patient population is small, incentives to manufacture can diminish rapidly and may result in drug shortages.[25]

Incentive for More Chemotherapy. Much has been written about the current fee-for-service reimbursement model that can drive the costs of care. In cancer treatment, intravenous chemotherapy administration is reimbursed well, which includes margins on the actual cost of the drug and reimbursement for chemotherapy suite hours, intravenous fluids, premedications, and antiemetics. Although we believe that physicians seldom treat patients who do not need treatment, the system does create a financial incentive to not only administer chemotherapy but to also potentially choose a more expensive drug when there is a choice for a cheaper alternative. For example, in an analysis of Medicare claims from 1995 to 1998 linked to the Survey, Epidemiology, and End Results cancer registry, the level of reimbursement did not affect physicians' decisions on whether to administer chemotherapy to patients with metastatic lung, breast, or gastrointestinal malignancies. However, it did affect the type of chemotherapy used. Physicians receiving more generous Medicare reimbursements (measured by calculating the difference between a physician's and the national mean reimbursement for each agent that the physician prescribed) used more costly treatment regimens.[26] In another study, the same authors reported that in response to a decrease in reimbursement for carboplatin and paclitaxel, prescribing practices shifted toward other drugs with higher margins.[27] Finally, Weight et al[28] suggest that a sharp decline in the use of medical androgen ablation in 2004 and 2005 was a result of changes in reimbursement due to the Medicare Modernization Act.

Lack of Thresholds for Clinical Benefit. Finally, there is no requirement for a minimum or reasonable magnitude of benefit. The FDA approves drugs based on evidence of clinical benefit and safety without a clear required threshold for magnitude of benefit needed in phase 3 trials to justify approval. With a large enough sample size, a statistically significant prolongation of overall survival can be shown even if the drug improves the life span only by a few days or weeks. Drugs can also be approved based on prolongation of surrogate end points, with no proof that patients will benefit from improved survival. The Patient-Centered Outcomes Research Institute, created by the Patient Protection and Affordable Care Act of 2010, is an independent, nonprofit organization whose research is designed to inform health care decisions using cost-effectiveness analysis. However, the Patient Protection and Affordable Care Act of 2010 specifically prohibits the Patient-Centered Outcomes Research Institute or the Secretary of Health from using cost-effectiveness mea-

Mayo Clin Proc. ■ October 2012;87(10):935-943 ■ http://dx.doi.org/10.1016/j.mayocp.2012.07.007
www.mayoclinicproceedings.org

sures to determine coverage, reimbursement, or incentive programs.[29]

However, the costs of health care are not increasing only in pharmaceuticals but in many areas, including hospitalizations and imaging.[30,31] In addition, many pharmaceutical companies have been generous in providing medications at low or no cost to qualifying patients. The cost of care is a system-wide problem that includes many participants, including health care professionals, device manufacturers, and medical supply manufacturers. These additional issues are beyond the scope of this commentary.

What Polices or Interventions Can Be Used to Lower the Cost of Cancer Drugs?

We believe that with some bold initiatives, the cost of cancer drugs and, indeed, cancer care can be managed such that we may improve outcomes for patients worldwide through greater accessibility and affordability of drugs while still allowing continued pharmaceutical innovation.

Value-Based Reimbursement and Pricing. As many other commentators have observed, we are of the belief that the current payment model in the United States is not sustainable and that reimbursement for medical care should be tied to discrete measurable metrics that reflect improved outcomes for a population. To better understand the link between improved population outcomes and cost savings, value-based pricing pilot programs are currently under way. For example, CareFirst BlueCross BlueShield of Maryland launched the Primary Care Medical Home program in 2010 with a goal to improve quality care and slow the rise of health care costs. If a primary care physician elects to participate in the program, the physician receives a 12% increase to the current reimbursement fee schedule, $300 dollars for creating and following a care plan for selected patients with chronic diseases, and shared savings from decreased health care expenditures over 3 years.

However, physicians are just one constituent influencing the cost of health care in the United States. Our partners in the pharmaceutical industry, device manufacturing, and industry supply must also commit to value-based pricing. We believe that these partners are rightfully profit-maximizing entities but that the price paid for products and services should be a reflection of the value they bring to the patient's health. For example, in the face of rising prescription drug costs, other developed nations, such as Canada and the United Kingdom, have price control measures in place. Owing to rising expenditures, Germany recently enacted the Pharmaceutical Market Restructuring Act in which the Joint Federal Committee (the paramount decision-making body) will be involved in negotiating prices for new drugs.[32,33]

Quality-Adjusted Life-Year and Incremental Cost-effectiveness Ratio. Value-based pricing is critical and requires an economic analysis of the benefit provided to the patient. Quality-adjusted life-years (QALYs)—the number of years of life that would be added by an intervention adjusted for quality of life—is a key metric that is commonly used in assessing the value for money of a drug or device. In essence, QALY takes into account the gained life expectancy and quality of life[34]: QALY = life expectancy $\times$ Q·Q is a quality of life value that ranges from 0.0 to 1.0. In perfect health, Q is considered to be equal to 1.0. A Q of 0.5 indicates a quality of life that is 50% of normal. Thus, a gain of 1 full year at a Q of 0.5 is equivalent to a gain of half a year in perfect health (QALY = $1 \times 0.5 = 0.5$ years). The value of Q for a given intervention is affected by the efficacy and toxicity of the therapy and is determined based on standardized measures, such as time trade-off, the standard gamble method, willingness to pay, visual analog scales, EuroQol's EQ-5D questionnaire,[35] the Quality of Well-being Scale,[36] or the years of healthy life measure.[37] In general, these measures include assessments of vision, hearing, mobility, cognition, speech, pain, dexterity, and emotion.

Once QALY is determined, the next step is to calculate the incremental cost-effectiveness ratio (ICER). Let us assume that for a serious, life-threatening condition, standard treatment costs $3000 and provides 1 year of life with an estimated Q of 0.4. The QALY associated with this treatment is, therefore, 0.4 years. Now let us suppose that a new treatment is developed that costs $50,000 and provides 2 years of life with a Q of 0.7. The QALY in this state is $2 \times 0.7 = 1.4$ years. The ICER is calculated by taking the difference in costs between the 2 treatments divided by the difference in QALYs between the two treatments: ICER = ($50,000-$3000)/(1.4-0.4) = $47,000 per QALY gained.

The ICER per QALY calculation is an important metric, but it does have some limitations that must be well understood when using the ICER to making decisions on drug approval or pricing. First, the QALY value by itself is variable based on the value assigned to Q. Because several different tools are used to determine the quality-of-life measurement Q, different QALY results may be calculated from each tool. Therefore, intermethod variation in the calculation of Q may lead to widely different QALYs. Furthermore, the estimation of QALY and ICER relies on clinical trials that often use surrogate end

points such as progression-free survival and disease-free survival that do not necessarily predict improved overall survival. Finally, patients involved in clinical trials are a selected group. When used in an unselected population, treatments may induce toxic effects at a rate greater than expected. Increased expenditure in the population may, thus, negate any cost benefit seen in clinical trials.[38]

Despite the previously mentioned limitations, the ICER per QALY is one of the major metrics that have been used in drug-approval decisions in some countries. To do this, the ICER per QALY cannot be considered in isolation. The calculated ICER needs to be compared with a threshold that has been determined to be acceptable by some entity, whether it be society, a patient, a physician, or a payer. In the United Kingdom, the desired ICER for approval of treatments for cancer is typically less than $50,000 per QALY; drugs have been disapproved for not having an acceptable ICER per QALY. A similar threshold is also used in Canada. In the United States, the ICER is not considered for regulatory approval, but one commonly held ICER threshold is $50,000 to $100,000, a range chosen many decades ago based on the approximate yearly cost of dialysis. However, investigators in a more recent analysis have estimated that the average ICER per QALY of dialysis in current practice compared with the next least costly alternative is $129,000, with a range of $65,496 to $488,360.[39] Furthermore, assessing the cost-effectiveness of a drug or intervention is just one part of a treatment plan that may include hospitalization costs, surgeries and procedures, radiotherapy, and indirect costs due to lost wages. It is, therefore, evident how difficult it is to establish a threshold ICER to help guide and formulate policy decisions.[40]

However, imperfections in cost-effectiveness analysis should not be an excuse for inaction. We believe that the previously mentioned analyses will help physicians better understand the expenditure implications of our medical decision making. It is akin to many other metrics, such as miles per gallon or energy efficiency ratios. On their own, QALY and ICER are not the sole metrics to be used in decision making, but having the information and using it in the appropriate context is much more powerful. It allows physicians and patients to have more meaningful discussions about treatments and allows patients to compare one treatment with another.

The "Value Dossier"and Pharmacovigilance. Because expenditure and quality-of-life data have been obtained during clinical trials, we recommend that the FDA be able to mandate that such materials be submitted in support of regulatory approval for a new drug. The FDA may continue to grant approvals based on efficacy and safety data, but the availability of cost and quality-of-life analysis sufficient enough to calculate and report Q, QALY, and ICER should ideally become part of the approval process in the United States as it is in some other developed countries. After approval of a drug, a population-based database should be established to continue to collect such data. This information would allow for comparisons across different drugs and would give patients and physicians the ability to make better informed decisions about treatments. The Drug Effectiveness Review Project is an example.[41]

The debate over value-based pricing in the United States (if it ever reaches a national level) for cancer drugs will probably be long and arduous. One can still hear phraseology such as "death panels" and "pulling the plug on granny" echoing in political discourse, and the discussion around the Supreme Court's decision to uphold the individual mandate as part of the taxing powers of Congress will continue to stir debate this election year. Therefore, it is unlikely that a pricing system such as Germany's will be enacted in the United States. However, allowing the Centers for Medicare and Medicaid Services to negotiate payments for drugs, devices, and interventions has the potential to bring health expenditures down as it has in other countries.[42]

One argument against price controls and value-based pricing is that these run counter to free market principles and the setting of prices based on supply and demand. We have already shown in the first section how cancer care is not representative of a "free market" system, and the traditional checks and balances that make the free market system work so efficiently in all other areas are absent when it comes to most cancer treatments. Another concern is that drug companies may refuse to lower prices and deprive US patients of new and potentially exciting treatments. We believe that this is unlikely. According to the Organisation for Economic Co-operation and Development, an organization composed of high-income, developed countries that defines itself as being committed to democracy and the market economy, the total expenditure on pharmaceuticals and other nondurables per capita is the highest in the United States among member countries.[43] The United States is a large, if not the largest, market, and the other nations in the Organisation for Economic Co-operation and Development have strong drug pricing regulations. We believe that pharmaceutical companies would still introduce these drugs in the United States because of our market size and negotiate a lower price to gain entry. As incredulous as this may sound, it seems to be happening in the United Kingdom. Learn and Bach[44] suggest that

drug companies have received approval for pemetrexed (Alimta; Eli Lilly & Co, Indianapolis, IN) in the United Kingdom by lowering the price and, therefore, improving the cost-effectiveness of pemetrexed (Alimta) to come under the National Institute for Health and Clinical Excellence's implicit cost-effectiveness and ICER thresholds for approval.

Improved National Guidelines. Current national cancer guidelines often present a list of all possible or acceptable treatment options for a given cancer, but they do not provide any kind of comparative analysis to enable patients and physicians to choose the most cost-effective option or the best option based on risks and benefits. There is a great need for national evidence-based guidelines that critically examine quality-of-life and mortality data, that assess benefits in light of not only risks but also cost, and that provide transparency on the most cost-effective option. This approach will highlight the cost utility of a proposed treatment and help patients and physicians make better informed treatment decisions.

Outside of guidelines, there must be a balance between physician autonomy in prescribing a treatment regimen and costs incurred by society. de Souza et al[45] describe evidence from a private-payer database that several enrollees received non–evidence-based medicine regimens for metastatic colon cancer at a substantial cost. In a cohort of 1041 patients, 140 received at least 1 non–evidence-based medicine regimen, with an estimated total drug cost for the patients and payers of $2,009,480, or $1930 per case.[45]

Create "Monopoly" Rules. In the United States, where there is an emphasis on market forces to regulate prices, value-based pricing for all drugs may not be necessary; we need price controls only in "monopoly" situations. We believe that when 2 (or more) similar drugs of the same class are available to treat a particular cancer, and provided that both are considered in the medical community to be equivalent, market forces may be sufficient to keep prices under control. However, a determination needs to be made at the time of a new drug approval whether the drug will operate in a monopoly environment. There are 3 suggested solutions we propose in this situation. First, drugs that are considered to be in such a niche will need to be subjected to price controls or more competition. For example, if a drug is approved for the treatment of an advanced cancer for which there is no cure and it is believed that at some point almost every patient with the given cancer will need that drug, it should be considered a monopoly even if multiple options exist for that cancer. Such drugs fulfill areas of unmet need; regardless of how many drugs are available for that indication, once a patient fails those options, they are back to square one. In such cases, the given monopoly drug should be subject to some legally mandated price control after the drug is approved. This process is best adjudicated by a panel of health care professionals who have no financial or nonfinancial conflicts of interest in the success of the drug. If a mandatory system is impossible to set up, at least a voluntary system could be set up in which pharmaceutical companies agree to such adjudication and imposition of price controls in exchange, for example, for expedited review or accelerated approval based on phase 2 studies and surrogate end points. Second, an important option for reducing monopoly situations is to approve additional drugs for the same indication based on equivalence and the same strength of data without a requirement to show superiority in safety or efficacy over the older approved drug (s). The free market principles can operate only when there are 2 or more equally good choices that can be used interchangeably; 2 drugs of different classes, such as bortezomib and lenalidomide, for multiple myeloma do not represent free market competition because both drugs are needed for patients with this cancer and the use of one does not negate the need for the other. A third option to consider if the previous 2 options are not possible is "compulsory licensing" for lifesaving drugs that are considered to be in a monopoly environment. Compulsory licensing is a strategy permitted under the Doha declaration of 2001 whereby, in the interest of public health, a country (usually a developing nation) grants a license to manufacture a drug that is still under patent protection to a low-cost generic company for use in that particular country. For example, because the cost of sorafenib (used to treat renal and liver cancer) was prohibitive, on March 12, 2012, the Indian government awarded a compulsory license to a generic company to manufacture the drug for use in India to provide a lower-cost alternative. Similarly, Brazil issued a compulsory license for the antiretroviral drug efavirenz after it failed to persuade the manufacturer of this drug to lower the cost to match its national resources. This option is now technically available to Canada and European countries as well.

Nonprofit Generic Companies. As long as we have a for-profit system involved in the manufacture of lifesaving drugs, we will always run the risk of high costs. In the next 10 years, numerous lifesaving cancer drugs will become generic, and there is an excellent opportunity to make these available at a very

low cost. However, the only way we might see the cost of generic cancer drugs approach the cost of manufacturing and distribution is to have philanthropic foundations step in and be involved in the actual manufacture (or importation) and delivery of lifesaving drugs. An extremely well-funded philanthropic foundation could, in theory, either create a nonprofit generic manufacturing company or purchase established generic manufacturing companies and make generic cancer drugs available at a very low cost because they would have no motive to profit from such a venture. Alternatively, they could facilitate FDA approval of companies that legally manufacture generic cancer drugs in other countries for a fraction of the cost at which the drug is sold in the United States. There are, of course, few philanthropic foundations in the world that have the resources to do any of this, and the idea is far-fetched. However, if someone steps forward, as happened in the case of providing drugs to treat human immunodeficiency virus and other diseases in Africa, we may be able to provide a segment of patients with accessible and affordable cancer drugs. In addition, the existence of nonprofit generic companies may also help prevent or deal with drug shortages.

Ultimately, we as a society must find a balance between health care affordability and profits that will provide the necessary incentive for continued innovation. Not doing so risks creating a health care system in which all participants lose.

ACKNOWLEDGMENTS

We thank Robert C. Wolf, PharmD, for assistance with estimation of the prices of the cancer drugs referenced in this article.

Correspondence: Address to S. Vincent Rajkumar, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (rajkumar.vincent@mayo.edu).

REFERENCES

1. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med*. 2010;363(8):711-723.
2. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011;364(26):2517-2526.
3. Meropol NJ, Schulman KA. Cost of cancer care: issues and implications. *J Clin Oncol*. 2007;25(2):180-186.
4. Leveque D. Off-label use of anticancer drugs. *Lancet Oncol*. 2008;9(11):1102-1107.
5. Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc*. 87(10):982-990.
6. Smith K, Jacobson G, Huang J, Neuman T. *Projecting Income and Assets: What Might the Future Hold for the Next Generation of Medicare Beneficiaries?* Menlo Park, CA: The Henry J. Kaiser Family Foundation; June 2011.
7. Himmelstein DU, Thorne D, Warren E, Woolhandler S. Medical bankruptcy in the United States, 2007: results of a national study. *Am J Med*. 2009;122(8):741-746.
8. Himmelstein DU, Thorne D, Woolhandler S. Medical bankruptcy in Massachusetts: has health reform made a difference? *Am J Med*. 2011;124(3):224-228.
9. McKee AE, Farrell AT, Pazdur R, Woodcock J. The role of the U.S. Food and Drug Administration review process: clinical trial endpoints in oncology. *Oncologist*. 2010;15(suppl 1):13-18.
10. Kaitin KI. The landscape for pharmaceutical innovation: drivers of cost-effective clinical research. *Pharm Outsourcing*. 2010; 2010(May):3605.
11. DiMasi JA, Grabowski HG. Economics of new oncology drug development. *J Clin Oncol* 2007;25(2):209-216.
12. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. *Clinic Pharmacol Ther*. 2010;87(3):272-277.
13. Ansell SM, Kyle RA, Reeder CB, et al. Diagnosis and management of Waldenström macroglobulinemia: Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) guidelines. *Mayo Clin Proc*. 2010;85(9):824-833.
14. Kohli M, Tindall DJ. New developments in the medical management of prostate cancer. *Mayo Clin Proc*. 2010;85(1):77-86.
15. Yoon HH, Khan M, Shi Q, et al. The prognostic value of clinical and pathologic factors in esophageal adenocarcinoma: a Mayo cohort of 796 patients with extended follow-up after surgical resection. *Mayo Clin Proc*. 2010;85(12):1080-1089.
16. Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc*. 2009;84(12):1095-1110.
17. Lust JA, Lacy MQ, Zeldenrust SR, et al. Induction of a chronic disease state in patients with smoldering or indolent multiple myeloma by targeting interleukin 1β-induced interleukin 6 production and the myeloma proliferative component. *Mayo Clin Proc*. 2009;84(2):114-122.
18. Moreno-Aspitia A, Perez EA. Treatment options for breast cancer resistant to anthracycline and taxane. *Mayo Clin Proc*. 2009;84(6):533-545.
19. Goldman DP, Joyce GF, Lawless G, Crown WH, Willey V. Benefit design and specialty drug use. *Health Aff (Millwood)*. 2006;25(5):1319-1331.
20. Bach PB. Limits on Medicare's ability to control rising spending on cancer drugs. *N Engl J Med*. 2009;360(6):626-633.
21. Simpson RJ Jr, Signorovitch J, Birnbaum H, et al. Cardiovascular and economic outcomes after initiation of lipid-lowering therapy with atorvastatin vs simvastatin in an employed population. *Mayo Clin Proc*. 2009;84(12):1065-1072.
22. Culler SD, Weintraub WS. Is initiation of atorvastatin for employees a good buy for employers? *Mayo Clin Proc*. 2009; 84(12):1059-1061.
23. Tan H, Sarawate C, Singer J, et al. Impact of asthma controller medications on clinical, economic, and patient-reported outcomes. *Mayo Clin Proc*. 2009;84(8):675-684.
24. Jabbour E, Cortes JE, Kantarjian HM. Suboptimal response to or failure of imatinib treatment for chronic myeloid leukemia: what is the optimal strategy? *Mayo Clin Proc*. 2009;84(2):161-169.
25. Gatesman ML, Smith TJ. The shortage of essential chemotherapy drugs in the United States. *N Engl J Med*. 2011;365(18): 1653-1655.

26. Jacobson M, O'Malley AJ, Earle CC, Pakes J, Gaccione P, Newhouse JP. Does reimbursement influence chemotherapy treatment for cancer patients? *Health Aff (Millwood)*. 2006; 25(2):437-443.
27. Jacobson M, Earle CC, Price M, Newhouse JP. How Medicare's payment cuts for cancer chemotherapy drugs changed patterns of treatment. *Health Aff (Millwood)*. 2010;29(7):1391-1399.
28. Weight CJ, Klein EA, Jones JS. Androgen deprivation falls as orchiectomy rates rise after changes in reimbursement in the U.S. Medicare population. *Cancer*. 2008;112(10):2195-2201.
29. The Patient Protection and Affordable Care Act. PL 111-148. March 23, 2010.
30. Karaca-Mandic P, McCullough JS, Siddiqui MA, Van Houten H, Shah ND. Impact of new drugs and biologics on colorectal cancer treatment and costs. *J Oncol Pract*. 2011;7(3 suppl): e30s-e37s.
31. Dinan MA, Curtis LH, Hammill BG, et al. Changes in the use and costs of diagnostic imaging among Medicare beneficiaries with cancer, 1999-2006. *JAMA*. 2010;303(16):1625-1631.
32. AMNOG (Arzneimittelmarktneuordnungsgesetz): law on realignment of the pharmaceutical market in Germany. http://www.articlesbase.com/vision-articles/amnog-arzneimittelmarktneuordnungsgesetz-law-on-realignment-of-the-pharmaceutical-market-in-germany-4119156.html. Accessed June 6, 2012.
33. AMNOG one year on: how will German health reform impact pharma market access in 2012? http://healthcare.blogs.ihs.com/2012/02/02/amnog-german-health-reform-pharma-market-access-2012/. Accessed June 6, 2012.
34. Sassi F. Calculating QALYs, comparing QALY and DALY calculations. *Health Policy Plan*. 2006;21(5):402-408.
35. EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
36. Kaplan RM, Anderson JP. A general health policy model: update and applications. *Health Serv Res*. 1988;23(2):203-235.
37. Erickson P, Wilson R, Shannon I. Years of healthy life. *Healthy People 2000 Stat Notes*. 1995;Apr(7):1-15.
38. Fraser J, Steele N, Al Zaman A, Yule A. Are patients in clinical trials representative of the general population? Dose intensity and toxicities associated with FE100C-D chemotherapy in a non-trial population of node positive breast cancer patients compared with PACS-01 trial group. *Eur J Cancer*. 2011;47(2): 215-220.
39. Lee CP, Chertow GM, Zenios SA. An empiric estimate of the value of life: updating the renal dialysis cost-effectiveness standard. *Value Health*. 2009;12(1):80-87.
40. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine: Panel on Cost-Effectiveness in Health and Medicine. *JAMA*. 1996; 276(14):1172-1177.
41. Neumann PJ. Emerging lessons from the Drug Effectiveness Review Project. *Health Aff (Millwood)*. 2006;25(4):W262-W271.
42. Gellad WF, Schneeweiss S, Brawarsky P, Lipsitz S, Haas JS. What if the federal government negotiated pharmaceutical prices for seniors? An estimate of national savings. *J Gen Intern Med*. 2008;23(9):1435-1440.
43. OECD (2012). OECD Health Data 2012. http://www.oecd.org/health/healthpoliciesanddata/oecdhealthdata2012-frequentlyrequesteddata.htm. Accessed June 7, 2012.
44. Learn PA, Bach PB. Pem and the cost of multicycle maintenance. *J Thorac Oncol*. 2010;5(8):1111-1112.
45. de Souza JA, Polite BN, Zhu S, et al. Utilization and costs of non-evidence-based (non-EBM) antineoplastic agents in patients with metastatic colon cancer (mCC). *ASCO Meeting Abstracts*. 2011;29:6002.