The Financial Burden and Distress of Patients with Cancer: Understanding and Stepping-Up Action on the Financial Toxicity of Cancer Treatment

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Abstract: “Financial toxicity” has now become a familiar term used in the discussion of cancer drugs, and it is gaining traction in the literature given the high price of newer classes of therapies. However, as a phenomenon in the contemporary treatment and care of people with cancer, financial toxicity is not fully understood, with the discussion on mitigation mainly geared toward interventions at the health system level. Although important, health policy prescriptions take time before their intended results manifest, if they are implemented at all. They require corresponding strategies at the individual patient level. In this review, the authors discuss the nature of financial toxicity, defined as the objective financial burden and subjective financial distress of patients with cancer, as a result of treatments using innovative drugs and concomitant health services. They discuss coping with financial toxicity by patients and how maladaptive coping leads to poor health and nonhealth outcomes. They cover management strategies for oncologists, including having the difficult and urgent conversation about the cost and value of cancer treatment, availability of and access to resources, and assessment of financial toxicity as part of supportive care in the provision of comprehensive cancer care.

Keywords: antineoplastic agents, costs and cost analysis, decision making, health financing, oncologists, precision medicine, referral and consultation, supportive care

Introduction

In 2013, about 120 experts in chronic myeloid leukemia penned an editorial drawing attention to the high prices of cancer drugs. 1 In this now widely cited piece, the authors from around the world rallied for the lowering of prices of cancer drugs to make them affordable to more patients. They discussed long-term health care policies to address the multiplicity of factors that impact drug prices. Two years later, a commentary signed by 115 American scientists, nearly all from the medical community, reiterated the urgency of addressing the spiraling prices of cancer drugs, ascribing potentially catastrophic clinical and health system consequences to these dramatic price increases. 2 Most recently, in June 2017, the American Society of Clinical Oncology (ASCO) released a position statement on the affordability of cancer drugs in which the professional group voiced concern about the pricing of oncology specialty drugs, including the problems of unaffordable coinsurance rates and high out-of-pocket (OOP) expenses. 3 Needless to say, there is much concern among oncology providers about cost barriers to innovative treatment, which undermine their efforts in providing high-quality and potentially lifesaving cancer care. Concern about access to, and affordability of, cancer treatment is widespread and shared by the wide community of clinicians, not only by a small group of pioneering medical oncologists and scientists. 4-6

At a time when patients with cancer and their advocates anticipate with great optimism the newer classes of cancer drug therapies, enthusiasm over next-generation targeted therapies and immune-oncology agents, as well as their
Expensive Cancer Drugs

That the issue of cancer drug prices is perhaps nowhere more pressing than in the United States is underpinned by the particularities pertaining to market authorization and reimbursement and health care financing and funding. Compared with other countries, more oncology drugs are available in the United States compared with other countries given the applications and regulatory approval and coverage decisions for new molecular entities as well as new indications for anticancer drugs in the United States.\(^1\)\(^,\)\(^1\)\(^2\)\n
Market access does not necessarily translate to patient access, however. Patient access to innovative cancer drugs is limited by the absolute and relative costs of treatment. Compared with patients who have cancer and are not receiving chemotherapy, the (per-person) expenditures of patients with cancer who are receiving chemotherapy are nearly 4-fold.\(^1\)\(^3\) Patients may bear a larger share of the costs of oral therapies compared with the costs of intravenous treatments, because the former are covered under the prescription drug benefit, while the latter are often covered under the medical benefit of most insurance plans, including Medicare.\(^1\)\(^4\)

Medicare Part D plans cover antineoplastic agents—along with 5 other so-called “protected” classes. Risk standard benefits include a $400 deductible and 25% coinsurance up to an initial coverage limit of $3700 in total drug costs, followed by a coverage gap (also referred to as the “doughnut hole”).\(^1\)\(^5\) During the gap, enrollees are responsible for a larger share of their total drug costs than in the initial coverage period, until their total OOP spending—or the unreimbursed, direct costs of treatment to individual patients—reaches the established threshold ($4950 in 2017). In the case of chronic lymphocytic leukemia, for example, it has been estimated that OOP costs for ibritinib treatment will amount to nearly $700 per month for this first-line therapy over 58 months.\(^1\)\(^6\) Table 1 shows the costs of a single month of treatment with oral targeted agents most recently approved by the US Food and Drug Administration (FDA).\(^1\)\(^7\)\(^-\)\(^2\)\(^1\)

Medicare-insured patients who are prescribed these therapies, which range from about $7500 to $25,000 monthly, can quickly reach the OOP maximum. Furthermore, for two-thirds of the newest oral targeted agents, 1 month of treatment exceeds the 2016 Federal Poverty Level (FPL) annual household income threshold for a one-person household (regardless of age).\(^2\)\(^2\) Unfortunately, high launch prices of cancer drugs are largely based on the prices of existing therapies (not necessarily competitors), rather than innovation or clinical effectiveness, such that patients may be paying exorbitant costs without the expectation of much benefit.\(^1\) Mailankody and Prasad reported that, among drugs approved during the period from 2009 through 2013, those approved based on response rate (RR) were priced higher compared with those approved on the basis of overall survival.\(^2\)\(^3\) Patients with cancer can expect to pay more for cancer drugs, whether they are next-generation agents or next-in-class. Indeed, not only are cancer drugs introduced at high prices, but prices also rise substantially postlicensing.\(^2\)\(^4\) An analysis by Howard et al of 58 anticancer drugs approved by the FDA between 1995 and 2013 indicated that launch prices, adjusted for inflation and drugs' survival benefits, increased by 10%, or about $8500, per year.\(^2\)\(^5\)

Cancer Drugs and Financial Toxicity

Understood as a side effect of cancer treatment akin to nausea and hair loss, the appeal and contribution of the term “financial toxicity” to the discussion of cancer drug prices are evident. Although cancer drugs are the key to gains in progression-free survival (if not overall survival) for a patient with cancer, their use may subject the patient to extreme financial burden and distress. Unfortunately, the concept of financial toxicity as it relates specifically to patients with cancer is not fully understood. Literature searches using the PubMed database conducted on September 23, 2017, for “financial toxicity,” “financial hardship,” and “financial distress” yielded 55, 433, and 152 results, respectively. Meanwhile, “financial toxicity” AND “cancer,” “financial hardship” AND “cancer,” and “financial distress” AND “cancer,” respectively, returned 44, 61, and 44 results.

Building on the framework proposed by Carrera and Zafar, financial toxicity can be conceptualized as the unintended—but not necessarily unanticipated—objective
financial burden on and subjective financial distress experienced by patients with cancer as a result of their treatment, particularly as they relate to newer classes of drugs and concomitant health services (see Fig. 1). It is consistent with existing frameworks, including those of Altice et al. on financial hardship and the PDQ Adult Treatment Editorial Board, which recognize both the material consequences of treatment and the psychosocial impact of cancer treatment.

**TABLE 1. US Food and Drug Administration-Approved Oral Cancer Drugs in 2016 to 2017 and Costs of Treatment**

| GENERIC NAME | BRAND NAME | CANCER TYPE | COST PER MONTH OF TREATMENT, US$ |
|--------------|------------|-------------|----------------------------------|
| Brigatinib   | Alunbrig   | NSCLC, ALK  | 12,868.76                        |
| Cabozantinib | Cabometyx  | Renal cell carcinoma, FLT3, KIT, MET, RET, VEGFR2 | 15,156.59                        |
| Enasidenib   | Idhifa     | Acute myeloid leukemia, IDH2 | 25,141.37                        |
| Midostaurin  | Rydapt     | Acute myeloid leukemia, FLT3 positive | 15,798.72                        |
| Neratinib    | Nerlynx    | Breast cancer, HER2 positive | 10,613.75                        |
| Niraparib    | Zejula     | Ovarian cancer, PARP1, PARP2 | 14,430.19                        |
| Ribociclib   | Kispali    | Breast cancer, HER2 negative | 8476.31                           |
| Rucaparib    | Rubraca    | Ovarian cancer, BRCA | 20,162.74                        |
| Venetoclax   | Venclexa   | Chronic lymphocytic leukemia, BCL2 | 7514.41                           |

Abbreviations: ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ER, estrogen receptor; FLT3, fms-related tyrosine kinase 3; HDAC, histone deacetylase; HER2, human epidermal growth factor receptor 2; IDH, isocitrate dehydrogenase; KIT, stem cell factor receptor; NSCLC, nonsmall cell lung cancer; PARP, poly(ADP-ribose) polymerase; VEGFR2, vascular endothelial growth factor receptor 2.

*Estimated monthly prices for chemotherapy drugs are based on the allowable Medicare charge and were calculated according to a methodology used by Dr. Peter B. Bach, Director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center, in a previously published article on cancer drug prices (Bach 2009). Since 2005, Medicare has reimbursed at 106% of the Average Sales Price (ASP) for Part B drugs. ASPs are reported in quarterly files released by the Center for Medicare and Medicaid Services. If a drug’s ASP is not available, then Medicare calculates the payment limit as 95% of the Average Wholesale Price (AWP). The AWPs were obtained using Thomson Healthcare’s Red Book (Thomson Healthcare 2010). For Part D drugs, current prices are retrieved from Medicare’s publicly available, Web-based “PlanFinder” tool (US Food and Drug Administration [FDA] 2017). The price we report for these drugs is the “Full Cost of Drug,” as reported in the PlanFinder for the Humana Enhanced Prescription Drug Plan, for a beneficiary living within zip code 10021. Payment limits for prior years vary and are described briefly in the table below and in more detail within the previously mentioned article. In all cases, the relevant payment limit is applied to a 12-week dosing regimen for an “average” adult weighing 70 kg, or with a body area of 1.7 m², and divided by 2.77 to arrive at a monthly price (on average, there are 2.77 months in 12 weeks). The 12-week dosing regimen is retrieved from the FDA-approved label for the drug, which are available in the FDA’s “Drugs@FDA” database (FDA 2017). The lowest total dosing regimen within the first FDA-approved indication for the drug is used in all cases. The prices shown are for the listed drug only; costs for supportive care or administration fees are not included.

**FIGURE 1. Conceptual Framework of Financial Toxicity in the Treatment of Patients With Cancer.** Financial toxicity results from both objective financial burden and subjective financial distress. The objective financial burden is due to the direct costs of cancer treatment, which increase over time from diagnosis. This financial burden is relative to the income and assets of the household of the patient with cancer, which decreases over time. Subjective financial distress ensues with mounting cancer-related expenditures and reduction in wealth combined with the anxiety and discomfort by the patient over their cancer experience. Adapted from: Carrera PM. The financial hazard of personalized medicine and supportive care. Paper presented at: Multi-national Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 2017 Annual Meeting; June 22-24, 2017; Washington, DC. Carrera PM, Zafar Y. Financial toxicity. In: The MASCC Textbook of Cancer Supportive Care and Survivorship. 2nd ed. New York: Springer; In press.
Objective financial burden stems from OOP spending on cancer drugs as well as treatment itself, including medical imaging, radiotherapy, surgery, and other procedures.\textsuperscript{26,29} Nonmedical costs associated with seeking treatment may be substantial if the patient with cancer and their caregiver need to travel and stay away from home regularly and for extended periods. Subjective financial distress results from the accumulation of OOP spending from the time of diagnosis, the erosion of the household's wealth and nonmedical budget, and worry about the effectiveness of coping strategies available to and used by the patient.\textsuperscript{26,30}

The financial burden of cancer treatment needs to be seen within the wider context of the patient's personal circumstances and experience with cancer diagnosis and treatment. It may be acute or chronic, depleting income and assets until these are ultimately exhausted. Furthermore, low-income patients, who generally have the lowest financial reserves with which to offset the financial burden of treatment, are at high risk of cancer-associated job loss. Blinder et al reported that the odds of job retention in patients with breast cancer whose annual household income was <200% of FPL was 0.25 compared with patients who had higher annual household incomes.\textsuperscript{31} Low-income workers in the United States are more likely to work in unsupportive work environments, with limited access to the workplace accommodations. For example, paid sick leave is available to only 21% of workers whose earnings are in the lowest 10% of incomes nationwide.\textsuperscript{32} Therefore, patients who can least afford to lose their jobs are at the highest risk of doing so.

Financial distress may be seen as distinct, but not isolated, from the overall anxiety and discomfort experienced by the patient with cancer as a result of the cancer diagnosis and its treatment.\textsuperscript{30,33,34} In a single-center survey of 120 patients with cancer, Meeker et al observed that financial distress was directly and indirectly associated with overall stress via mediation by emotional distress.\textsuperscript{33} In its 2008 report titled Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs, the Institute of Medicine (now the National Academy of Medicine of the National Academies of Sciences, Engineering, and Medicine) described the construct of financial stress as resulting from the cost of health care, low income, or a lack of health insurance.\textsuperscript{34} Coupled with the emotional distress associated with the cancer experience, financial distress from mounting financial obligations and debt and the erosion of wealth may interfere with the patient's ability to cope effectively with cancer, its physical symptoms, and its treatment, thereby adversely affecting health outcomes.\textsuperscript{33-35}

A Household Economic Perspective on Financial Toxicity

To best understand the concept of financial toxicity and underscore its significance in the discussion of the prices of drugs and health services in the United States, it is vital to take into account the treatment-related economic consequences and health outcomes experienced by the patient resulting from treatment as well as the patient's means of coping. In this section, we elaborate on the pathway to financial toxicity and the distal and proximal consequences of financial toxicity. Compared with the PDQ Adult Treatment Editorial Board framework,\textsuperscript{28} we highlight the important, multifaceted, and complex role of coping on the relationship between the different causative factors and financial toxicity. For example, maladaptive coping can decrease costs but, at the same time, worsen disease outcome. In reference to the framework of Altice et al,\textsuperscript{27} we elaborate on different coping mechanisms and how each plays a different role in the framework, depending on the situation.

As illustrated in Figure 2, the decision to seek medical care after the development of signs and symptoms of disease is influenced by the individual's health insurance coverage.\textsuperscript{10,36,37} In the absence of health insurance coverage, many forgo cancer screening and/or delay diagnosis and are thus likely to experience poor clinical outcomes, including higher cancer-specific mortality.\textsuperscript{37,38} Patients who have health care plans that require significant cost-sharing because of high deductibles and/or high coinsurance face similar barriers in access to timely and comprehensive cancer care, given the insufficient financial protection from medical expenditures.\textsuperscript{36,37,39} Thus, as the patient with cancer undergoes treatment, he or she faces an accumulation of direct medical and surgical costs.

The patient's household may try to cope with this accumulation of medical bills, given liquidity constraints, by reducing the use of other goods and services. Other lifestyle-changing, and potentially maladaptive, coping mechanisms include the use of savings, disposal of assets, and borrowing money or carrying a credit-card balance.\textsuperscript{40-42} Such coping mechanisms are implemented when income streams are limited, if not exhausted, by the inability of the primary income earner to maintain full employment or retain/return to gainful employment. Long treatment regimens are likely to exacerbate the problem, particularly in the case of chronic and/or metastatic cancer. It is worth underscoring that treatment decisions are made by patients with and/or in consideration of their families, because the economic impact of the cancer affects the whole family.\textsuperscript{36,37,43}

Among patients who are heads of households, spending decisions will likely take into consideration the household’s economic welfare.\textsuperscript{42,43} The downscaling of the standard of living and the accumulation of debt have implications for quality of life (QOL) and may engender maladaptive coping strategies with clinical implications.\textsuperscript{44,45} Medication nonadherence (dose delays and/or modifications that are not
clinically indicated and, in the case of oral drugs, treatment cessation) is one such maladaptive coping strategy with the potential to result in adverse clinical outcomes. From an economic perspective, intentional nonadherence (in contrast to unintentional nonadherence typically described among older patients and those with multiple comorbid conditions) provides cost savings for the patient. The decision to miss, avoid, or stop treatment altogether to mitigate the financial burden of cancer treatment may diminish the financial impact of treatment, but it does not eliminate it entirely, and it may have devastating clinical consequences. In the sections below, we have summarized the evidence about the financial burden on and financial distress experienced by patients with cancer.

Evidence About Financial Burden on and Financial Distress by Patients With Cancer

There have been no large studies of financial toxicity as a composite of objective financial burden and subjective financial stress among patients with cancer undergoing treatment, particularly as it relates to the newer classes of drugs. Gordon et al conducted a systematic review of financial toxicity among cancer survivors and identified 25 relevant studies: 14 were from the United States, 18 were cross-sectional, and the rest were prospective or retrospective cohort studies. Those authors reported that 28% to 48% of cancer survivors experienced financial toxicity using monetary measures (covering actual OOP spending and percentage of OOP spending to income ratios), and 16% to 73% experienced financial toxicity using subjective measures. Determinants of financial toxicity included being female, low income at baseline, loss of income, younger age, adjuvant therapies, antineoplastic therapies, more recent diagnosis, advanced cancer, no health insurance, and distance from treatment centers. It should be noted that, although Gordon et al defined subjective measures as those pertaining to perceptions of cancer-related financial burden and psychological impact, they defined objective measures as questions about tangible solutions to ease financial burden. In other words, objective measures referred to outcomes and coping mechanisms of individuals, which covered treatment nonadherence, longer delays in care, forgoing care, and loss of or change in insurance coverage.

The pilot study by Zafar et al on OOP expenses and the experience of insured patients with cancer, coupled with validation of the COmprehensive Score for financial Toxicity (COST) measure as a clinically relevant, patient-centered tool to measure financial toxicity, serves as a foundation for building up the empirical evidence. Briefly, the COST is an 11-item measure of financial toxicity covering a single financial item, 2 resources items, and 8 affect items. Lower COST values indicate more financial toxicity. In a cohort of 233 patients with advanced cancer from 2 cancer
centers in the Chicago metropolitan area, the COST measure demonstrated high internal consistency and test-retest reliability. Unemployment, nonwhite race/ethnicity, low income (defined as ≤200% of the FPL), higher psychological distress, and ≥3 inpatient admissions were significantly associated with financial toxicity when controlling for age, sex, marital status, insurance type, clinical trial participation, and communication preference.

In the pilot study by Zafar et al, 42% of 246 patients with solid tumors receiving chemotherapy or hormonal therapy reported subjective significant or catastrophic financial burden from cancer-related OOP expenses. Focusing on those who sought copayment assistance (n = 128), 46% reported subjective significant or catastrophic financial burden. For an objective measure of financial toxicity, they estimated OOP spending of patients based on cost diaries, which patients completed as part of the study, and found that, among patients who did not request copayment assistance (n = 31), median monthly OOP costs were $708 (interquartile range, $330-$1300). Interestingly, the median proportion of income spent OOP did not differ significantly between copayment applicants and nonapplicants. Consequently, the authors underscored the importance of the subjective assessment to identify patients who may benefit from intervention. Finally, they estimated the number of patients who were underinsured, which they defined as those who had OOP spending greater than 10% of their annual household income. They found that 55% of 159 individuals who completed at least one cost diary were underinsured.

Shankaran et al examined the treatment-related costs and financial experiences of 284 patients diagnosed with stage III colon cancer between 2008 and 2010 in Washington state. Participants were identified from the Cancer Surveillance System, which is part of the Surveillance, Epidemiology, and End Results program of the National Cancer Institute. The authors found that 38% reported at least one treatment-related financial burden, which the authors defined as accrual of debt, sale or refinancing of home, borrowing of money from friends or family, or ≥20% decline in annual income as a result of treatment-related expenses. In a univariate analysis, age <50 years (odds ratio [OR], 30.7; 95% confidence interval [95% CI], 6.6-143.9; P < .001); work disability, leave-of-absence, or unemployment (OR, 5.6; 95% CI, 2.4-13.3; P < .001); and an annual household income ≤$30,000 (OR, 4.1; 95% CI, 2.2-9.1; P < .001) were significantly associated with increased odds of financial hardship. Meanwhile, widowed marital status (OR, 0.08; 95% CI, 0.01-0.6; P < .001), Medicare (with supplemental) insurance (OR, 0.3; 95% CI, 0.2-0.6; P < .001), and retirement were all associated with decreased odds of financial hardship.

In their directed content analyses of narratives from 252 patients with colorectal cancer, Thomson and Siminoff reported similar results among 84 patients who were identified as facing financial barriers and for whom health insurance status was a hurdle to seeking medical care for their cancer symptoms. The patients who experienced such financial barriers were younger, reported a lower income, and were more likely to be unmarried compared with the full study sample. Indeed, unlike most younger patients with cancer, patients who are older than 65 years are eligible for Medicare coverage. The qualitative study of Thomson and Siminoff, as such, supports the observation of Shankaran et al that younger patients may have more difficulty than older individuals in adjusting to the financial pressures of cancer care because of higher baseline household expenses and having had less time to accumulate assets.

Finally, Medicare beneficiaries who have cancer spend a greater proportion of their, often fixed, incomes on OOP medical costs compared with those without cancer. In a retrospective, observational study that pooled data from the Medicare Current Beneficiary Survey linked to Medicare claims (1997-2007), Davidoff et al found that Medicare beneficiaries with cancer (n = 1868) faced a higher OOP burden than their counterparts without cancer (n = 10,047). Specifically, patients with cancer had higher mean OOP costs compared with beneficiaries without cancer ($4727 and $3209, respectively; P < .001). Receipt of radiation and antineoplastic therapy were associated with higher OOP spending ($1526 and $1470, respectively; P < .01), which accounted for 36.4% and 31.0% of the OOP expenses for cancer treatment. As a share of income, mean total OOP was likewise higher for Medicare beneficiaries with cancer (23.9% and 14.1%, respectively; P < .001). Interestingly, because beneficiaries with income 100% to 200% of the FPL experienced $1127 higher spending compared with those living below the FPL, a large percentage of OOP spending for beneficiaries with cancer appear to be associated with treatments covered through the Medicare medical benefits.

Evidence on Outcomes of Financial Toxicity

The abandonment, delay, and discontinuation of treatment form part of the arsenal of strategies that patients with cancer use to cope with the financial burden of treatment. Streeter et al, in their analysis of abandonment of newly initiated oral oncolytics in 10,508 patients with Medicare and commercial insurance for whom oral oncolytic therapy was initiated between 2007 and 2009, found that claims with cost sharing >$500 were 4 times more likely to be abandoned than claims with cost sharing ≤$100 (OR, 4.46; P < .001). Compared with capcitabine, sorafenib and imatinib were 5 times and 2 times more likely to be abandoned, respectively (OR, 4.87 and 2.09, respectively; P < .001). Meanwhile, in their examination of 3781 Medicare
beneficiaries, Kaisaeng et al found that beneficiaries delayed or discontinued treatment once they reached a mean ± standard deviation OOP spending level of $4210 ± $2161 for imatinib, $3634 ± $2147 for erlotinib, and $4032 ± $4032 for thalidomide. The annualized OOP costs were $8359 for imatinib, $10,348 for erlotinib, and $13,677 for thalidomide. A large majority of patients who received the more expensive drugs entered the coverage gap at the time of their first prescription fill, including 88% of those who received imatinib (n = 123), 99% of those who received erlotinib (n = 96), and 98% of those who received thalidomide (n = 97).

Zafar et al reported that, regardless of whether or not patients with cancer requested copayment assistance, they engaged in lifestyle-changing strategies, such as reducing spending on food and clothing (53% and 27%, respectively; P < .001) and borrowing money or using credit to pay for medications (49% and 20%, respectively; P < .001). Patients with cancer also altered the way they obtained their medications, including obtaining samples from a physician (63% and 30%, respectively; P < .001) and price shopping (for cancer drugs) from available pharmacies (54%, and 27%, respectively; P < .001).

Lathan et al observed a clear dose-response relationship between decreasing financial reserves and all measures of well being using the 12-item Short Form Health Survey (SF-12) physical and mental health scales to measure overall QOL, the EuroQol-5 Dimension (EQ-5D) scale for health-related QOL, the Brief Pain Inventory to measure pain, and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 Symptom Inventory for symptom burden. They found that, relative to patients who had more than 12 months of financial reserves, those who had limited financial reserves (of ≤2 months) reported poorer QOL. In addition, Fenn et al examined the association between cancer-related financial problems and QOL based on the 2010 National Health Interview Survey. In a sample of 2108 patients with cancer, 9% reported “a lot” of financial problems, 12% reported “some,” 10% reported “a little,” and 70% reported “not at all.” Patients who reported that cancer caused “a lot” of financial problems had a 4-fold decrease in the likelihood of reporting excellent, very good, or good QOL (OR, 0.24; 95% CI, 0.14–0.40; P < .001). On the basis of these findings, the authors highlighted the potentially powerful impact of economic burden on the patients’ perception of their overall well being.

In the extreme case, financial burden may lead to personal bankruptcy. In their study on the incidence and time course of bankruptcy filings among patients newly diagnosed with cancer, Ramsey et al observed that Washington state patients with cancer were at 2.65 times greater risk of declaring personal bankruptcy than those without cancer. Patient with lung, thyroid, and colorectal cancer had 3.8, 3.46, and 3.02 greater odds (P = .05) of declaring personal bankruptcy than those without cancer. Hackney et al claim that the actual proportion of medical bankruptcies among all bankruptcies exceeded 50% in their analysis of data from a single US Bankruptcy Court district in which they accounted for misclassification resulting from selecting a population whose medical care was extremely expensive or from choosing ad hoc thresholds for medical bankruptcy categorizations. Finally, among cancer survivors, the adjusted hazard ratio for mortality among those who filed for bankruptcy versus those who did not was 1.79 (95% CI, 1.64–1.96; P < .001).

Colorectal cancer and prostate cancer survivors who declare bankruptcy have more than twice higher odds of death than those who do not (2.47 and 20.7, respectively; P < .001).

The Role of Clinicians in Managing Financial Toxicity

Oncologists and other clinicians have been leading voices in the discussion of patient access to lifesaving health care, and they are increasingly vocal on the issue of the affordability of cancer drugs. They have offered concrete solutions, including (but not limited to) encouraging the development and use of generics and biosimilars, transparency in drug costs, negotiation of drug prices by Medicare, as well as high-value drug development. In the latter, ASCO suggests that, to achieve a clinically meaningful outcome, a minimum incremental improvement in median overall survival over standard therapy needs to range between 2.5 and 6 months, depending on the clinical context (metastatic pancreatic, nonsmall cell lung, triple-negative breast, and colorectal cancers).

To complement these efforts at the US health care system level (a long-term undertaking involving other key stakeholders), and considering the critical nature of and evidence on financial toxicity, it is important to elaborate on the role of clinicians collectively in dealing with financial toxicity at the hospital level and as part of the multidisciplinary team of oncology care providers. This includes the difficult and urgent matter of discussing costs of treatment with the patient. In the context of patient-centered cancer care, the clinician plays a central role not just in the delivery of high-quality medical treatments but also in helping contain the financial burden and distress to an individual patient with cancer in the short term, and for all patients with cancer in the long term. More than anyone in the multidisciplinary team of care, the oncologist may be the professional most able to integrate the diverse components of patient care. In their narrative review, Wein, Sulkes, and Stemmer highlight...
the central role of oncologists in the coordination of different aspects of patient care.62

As illustrated in Figure 3, the clinician is at the interface between health insurers and the cancer center and thus may advocate on behalf of their patients, ideally as a collective.2,3,10 There are various action points toward mitigating the financial toxicity of cancer treatment. In the context of patient-centered care, medical oncologists play a pivotal role not just in the delivery of high-quality treatment. They also serve as a focal point in helping contain the financial burden and distress of their respective patients, both in the short term and for all patients with cancer in the long term.63-65

FIGURE 3. Action Points for Mitigating Financial Toxicity in Patient-Centered Cancer Care. There are various action points toward mitigating the financial toxicity of cancer treatment. In the context of patient-centered cancer care, medical oncologists not only play a pivotal role in the delivery of high-quality treatment, but they also serve as a focal point in helping contain the financial burden on and financial distress of their respective patients, in the short term and for all patients with cancer in the long term. NCI indicates National Cancer Institute. Adapted from: Tefferi A, Kantarjian H, Rajkumar SV, et al In support of a patient-driven initiative and petition to lower the high price of cancer drugs. Mayo Clin Proc. 2015;90:996-1000; American Society of Clinical Oncology (ASCO). ASCO Position Statement on Addressing the Affordability of Cancer Drugs, ascoc.org/advocacy-policy/asco-in-action/asco-offers-path-addressing-affordability-cancer-drugs-new-position. Accessed July 13, 2017; Carrera PM. The financial hazard of personalized medicine and supportive care. Paper presented at: Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) 2017 Annual Meeting; June 22-24, 2017; Washington, DC.18

between 2014 and 2017 in awareness of the Choosing Wisely campaign among physicians (awareness increased from 21% to 25%).66 They also indicated that physician-reported difficulty in talking to patients about avoiding a low-value service remained steady (42% reported that such conversations had gotten harder in 2014, and 46% did so in 2017). In the section below, we touch upon the matter of the value of treatment to the patient given financial toxicity. Meanwhile, in their chronicle of Choosing Wisely’s progress since launch, Kerr et al noted that several studies showed either miniscule decreases or increases in the delivery of targeted low-value services.67

Focusing on cancer drugs, the decision of Memorial Sloan Kettering Cancer Center in New York to treat patients who have advance-stage colorectal cancer with either ziv-aflibercept or bevacizumab is an illustrative example of a high-impact intervention.68 After the approval of ziv-aflibercept for the treatment of advanced colorectal cancer in 2012 and with studies that suggested that ziv-aflibercept was equivalent in efficacy but twice as expensive as the existing drug bevacizumab, Memorial Sloan Kettering Cancer Center decided not to stock ziv-aflibercept.68 In fact, by drawing public attention to their action, they may well have precipitated the drug maker’s subsequent reduction in the price of ziv-aflibercept by one-half. Nonetheless, as Fleck and Danis argue, within their own hospitals, clinicians can make a big difference in the inclusion (or exclusion) of cancer drugs as part of their accountable care organizations’ bundled treatment plans.69 Indeed, Hunter et al, in their retrospective analysis of dialogues from 1755
TABLE 2. Avoiding Low-Value Treatment to Minimize Financial Toxicity in Patients With Cancer

| ASCO 2017<sup>63</sup> | ASTRO 2017<sup>64</sup> | COC 2017<sup>65</sup> |
|------------------------|------------------------|------------------------|
| **Don’t use cancer-directed therapy for patients with solid tumors who have the following characteristics:** low PS (3 or 4), no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anticancer treatment. | **Don’t initiate whole-breast radiotherapy as a part of breast-conservation therapy in women age ≥50 y with early stage, invasive breast cancer without considering shorter treatment schedules.** | **Don’t perform surgery to remove a breast lump for suspicious findings unless needle biopsy cannot be done.** |
| **Don’t perform PET, CT, or radionuclide bone scans in the staging of early prostate cancer at low risk for metastasis.** | **Don’t initiate management of low-risk prostate cancer without discussing active surveillance.** | **Don’t initiate surveillance testing after cancer treatment without providing the patient a survivorship care plan.** |
| **Don’t perform PET, CT, or radionuclide bone scans in the staging of early breast cancer at low risk for metastasis.** | **Don’t routinely use extended fractionation schemes (>10 fractions) for palliation of bone metastases.** | **Don’t use surgery as the initial treatment without considering presurgical (neoadjuvant) systemic and/or radiation therapy for cancer types and stages in which it is effective at improving local cancer control, QOL, or survival.** |
| **Don’t perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.** | **Don’t routinely recommend proton beam therapy for prostate cancer outside of a prospective clinical trial or registry.** | **Don’t perform major abdominal surgery or thoracic surgery without a pathway or standard protocol for postoperative pain control and pneumonia prevention.** |
| **Don’t use white cell-stimulating factors for the primary prevention of febrile neutropenia in patients with <20% risk for this complication.** | **Don’t routinely use IMRT to deliver whole-breast radiotherapy as part of breast-conservation therapy.** | **Don’t initiate cancer treatment without defining the extent of the cancer (through clinical staging) and discussing with the patient the intent of treatment.** |
| **Don’t give patients antiemetic drugs intended for use with a regimen that has a high risk of causing nausea and vomiting if they are starting on a chemotherapy regimen that has a low or moderate risk of causing nausea and vomiting.** | **Don’t recommend radiation after hysterectomy for endometrial cancer in patients with low-risk disease.** | **Don’t initiate noncurative radiation therapy without discussing with the patient the intent of treatment.** |
| **Don’t use combination chemotherapy (multiple drugs) instead of chemotherapy with one drug when treating an individual for metastatic breast cancer unless the patient needs a rapid response to relieve tumor-related symptoms.** | **Don’t routinely offer radiation therapy for patients who have resected NSCLC with negative margins and N0-N1 disease.** | **Don’t initiate noncurative radiation therapy without defining the goals of treatment with the patient and considering palliative care referral.** |
| **Avoid using PET or PET-CT scanning as part of routine follow-up care to monitor for a cancer recurrence in asymptomatic patients who have finished initial treatment to eliminate the cancer unless there is high-level evidence that such imaging will change the outcome.** | **Don’t initiate noncurative radiation therapy without defining the goals of treatment with the patient and considering palliative care referral.** | **Don’t initiate noncurative radiation therapy without defining the goals of treatment with the patient and considering palliative care referral.** |
| **Don’t perform PSA testing for prostate cancer screening in men with no symptoms of the disease when they are expected to live <10 y.** | **Don’t routinely recommend follow-up mammograms more often than annually for women who have had radiotherapy after breast-conserving surgery.** | **Don’t initiate noncurative radiation therapy without defining the goals of treatment with the patient and considering palliative care referral.** |
| **Don’t use a targeted therapy intended for use against a specific genetic aberration unless a patient’s tumor cells have a specific biomarker that predicts an effective response to the targeted therapy.** | **Don’t routinely add adjuvant whole-brain radiation therapy to stereotactic radiosurgery for limited brain metastases.** | **Don’t initiate noncurative radiation therapy without defining the goals of treatment with the patient and considering palliative care referral.** |

Abbreviations: ASCO, American Society for Clinical Oncology; ASTRO, American Society for Therapeutic Radiology and Oncology; CT, computed tomography; COC, Commission on Cancer; IMRT, intensity-modulated radiotherapy; NSCLC, non-small cell lung cancer; PET, positron emission tomography; PS, performance status; PSA, prostate-specific antigen; QOL, quality of life.

<sup>63</sup> The lists of common medical tests, treatments, and procedures by ASCO, ASTRO, and COC, respectively, that providers and patients should question are initiatives of the American Board of Internal Medicine Foundation, which seeks to advance a national dialogue about avoiding wasteful or unnecessary medical tests, treatments, and procedures (see Table 3).<sup>64</sup> Targeted therapy, immunotherapy, chemotherapy; <sup>65</sup> Imaging, radiotherapy; <sup>66</sup> Surgery; <sup>67</sup> Diagnostic, surveillance testing.

outpatient visits in community-based practices nationwide from 2010 to 2014 (which involved 677 patients who had breast cancer), noted that one of the strategies to reduce OOP costs involved switching from oral therapies with high copays (eg, ibandronic acid, alendronate sodium) to intravenous infusion therapies (eg, zoledronic acid), which were described as having little or no copays.<sup>70</sup>

Talking About Financial Toxicity

Granted that clinicians serve as their patients’ advocates, perhaps the bigger challenge is in confronting financial toxicity in the consultation room, for which the American Cancer Society has developed a list of questions that patients may want to bring up with their clinicians (see Table 3).<sup>71</sup> This may be seen as an opportunity to hold the
difficult but urgent conversation on the cost and value of cancer treatment and the availability of and access to resources. Such a probing question proposed by Koo et al as “Some patients want to know everything about their medical care: What is your preference?” may inform what and how much patients would like to know regarding their treatment.\textsuperscript{72} While some patients may be reluctant to bring up any difficulties they might have in paying for their treatment, most patients desire such a discussion as part of a trust relationship.

In their review of the literature on attitudes toward and conduct of cost communication between patients with cancer and oncologists, Shih and Chien noted that, in 8 studies that surveyed or interviewed patients’ attitudes toward cost communication the mean (weighted) and median proportions of patients who expressed a positive attitude toward cost discussions were 60\% and 61\% (n = 1006), respectively.\textsuperscript{73} Furthermore, based on 2 studies that inquired about physician comfort level toward cost communication, they found that, although 75\% of physicians (n = 199) considered discussions of OOP costs with patients their responsibility in one study; in another study, only 28\% of clinicians (n = 18) felt comfortable with such communication.\textsuperscript{73}

Shankaran and Ramsey proposed that making “financial health” a routine part of clinical assessment may help overcome the reluctance associated with discussing personal finances, identify patients at greatest risk for high financial burden, and prompt earlier financial assistance.\textsuperscript{74} The risk for financial toxicity can be informed by available information about a patient’s personal circumstances, including insurance coverage, age and marital status, place of residence, and distance from specialized treatment facility, based on their electronic health records.\textsuperscript{15} This can be coupled with the use of instruments such as the Distress Thermometer and Problem List, Patient Health Questionnaire-4, and the Hospital Anxiety and Depression Scale in screening for psychosocial distress.\textsuperscript{75-78}

Screening for risk of financial toxicity or assessment of financial toxicity using the COST measure may help inform the content and timing of a multicomponent intervention on par with diagnosing and relieving pain, nausea, and fatigue.\textsuperscript{26,77,78} Whereas the Union for International Cancer Control and the International Psycho-Oncology Society have endorsed distress as the sixth vital sign after pain,\textsuperscript{76} the focus of an intervention for financial distress will arguably differ from one that is mainly focused on financial burden and material lack of financial resources. With routine screening for and treatment of distress found to be feasible,\textsuperscript{78} a step up to addressing financial toxicity in daily practice involves the availability and comprehensiveness of supportive care and the support of management across cancer care facilities. Efforts will be disparate and unsustainable without a coordinated and comprehensive approach given the unintended consequences for cancer centers, hospitals, and networks.\textsuperscript{10}

**Supportive Care in the Management of Financial Toxicity**

In patient-centered cancer care, supportive care or palliative care is offered to the patient early and continues through the transition to end-of-life and hospice care.\textsuperscript{77} The expansion of supportive care is of great importance considering the projected increase in the absolute number of elderly patients with cancer in the coming years, the high incidence rate of thyroid cancer among women, and increasing incidence rates for liver cancer among men and women.\textsuperscript{79} The breadth of services that will be delivered to the patient in the management of financial toxicity will depend on the individual patient’s circumstances, and the capacity of the supportive care team. In any case, the “ask, tell, ask” approach promoted in the practice of supportive care in oncology will facilitate the discussion of financial toxicity.\textsuperscript{80} To be sure, the integration of supportive care in oncology is a work in progress and thus may be leveraged in the management and control of financial toxicity.\textsuperscript{81-84} Ramchandran et al, in their evaluation of the evidence on the integration of supportive care into oncology care, found that, although most US cancer centers have a supportive care program, the scope of supportive care remains limited.\textsuperscript{84}

The Oncology Care Model currently in trial, which aims toward more highly coordinated oncology care and an alignment of payment between commercial payers and Medicare, may help in the integration of supportive care in oncology, especially where the results show improved patient experience or health outcomes at lower cost.\textsuperscript{85} Perhaps the greater constraint in screening for financial toxicity as part of the supportive services offered is the availability of services to help the patient manage both the objective financial burden and the subjective financial distress of cancer treatment.\textsuperscript{10,26} In the section above, we underscored the importance of having a conversation about financial toxicity and the readiness of the clinician not just to engage in it but also the willingness to start it. It should be noted that, in the delivery of supportive services for the management of financial toxicity, a team is required (and, in various hospitals, is already in place) that may offer opportunities for identifying best practices based on results.\textsuperscript{86-88}

The team that provides supportive care may include a social worker and/or a nurse/patient navigator who may
best address treatment-related financial issues and/or is tasked with helping the oncologist in addressing financial burden issues of the patient with cancer. A review of studies on patient navigation in the hospital setting, it is worth noting, indicated that such strategies provide practical assistance, emotional empowerment, and informational support to patients with cancer. If the patient is concerned with being able to afford the copayment for oral cancer drugs, for example, then referral to programs that assist with oral cancer medications is a common course of action. Nonetheless, it should be noted that, although drug manufacturers’ copay assistance and coupon programs may offset patients’ OOP costs for cancer drugs, they are short-term, short-sighted solutions that help keep drug prices high. They may help the individual patient in question, but they also help maintain high drug prices by keeping the market price of the drug above the level that patients and/or insurance companies are willing and able to pay.

Conclusions

Comprehensive oncology care combines treatment of the cancer and management of treatment-related toxicities. Unlike clinical toxicities, financial toxicity is a potentially devastating consequence of cancer treatment that patients have often been left to manage on their own. Fortunately, clinicians and researchers alike have become increasingly aware of the need for interventions to address this problem. To inform these, and to ensure a comprehensive approach, more research is needed on various areas to fill evidence gaps, as pointed out by the PDQ Adult Treatment Editorial Board. As we have noted in this review, cancer drugs are not the only sources of financial toxicity, and modalities of treatment impose various objective financial burdens on the patient with cancer. Further studies are required on the role of diagnostic tests and imaging on financial toxicity and the outcomes of mechanisms used by patients to cope. We likewise have noted that, compared with middle aged patients with cancer, the elderly may be at lower risk for financial toxicity given Medicare coverage. In consideration of the expansion of the Affordable Care Act and the spread of high-deductible plans, additional research is needed to identify any subgroups of patients who may be at high risk for financial toxicity.

As we move forward with the development of these interventions, we must acknowledge the role that the various relevant stakeholders can play, including patients, clinicians, researchers, and policy makers. The management of financial toxicity must address the root causes of financial burden and financial distress as much as possible. A multipronged and sustainable approach may involve discouraging coupon programs over time while encouraging outcomes-based pricing and reimbursement and value-based formulary decision making. This process may include, for example, discussing the merits of infusion over oral cancer drugs (for which oncologists have much influence on the OOP spending of patients) with individual patients who, meanwhile, may assume that the convenience of oral cancer medication is worth their premium prices. From the clinician’s perspective, reimbursement for time and effort spent in discussing the costs of care with patients, shared decision making, patient education, treatment navigation, and palliative care is poor, and the level of reimbursement for chemotherapy administration is vulnerable to adverse policy changes. Clinicians who help shield their patients from the risk of financial toxicity fulfill their roles as loyal patient advocates as well as stewards of common-pool resources. However, they cannot take on the problem of financial toxicity alone.

This brings us back to the related tasks of advocating for the patient with cancer at the health system level while at the same time taking action at the hospital level and working with the patient in the consultation room. In addition to approvals for new molecular drugs, we can anticipate more FDA approvals for new indications for many innovative cancer drugs as precision medicine advances further. Inasmuch as we should be celebrating the fruits of our collective work in advancing the science of oncology, as custodians of patient-centered cancer care, we are concerned about whether our patients will benefit or be priced out of the market because of high OOP costs for cancer drugs and high insurance premiums, which incorporate higher spending projections on cancer treatment. As our armamentarium of effective

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**TABLE 3. Questions Patients With Cancer May Want to Ask About Treatment Costs**

- I'm worried about how much cancer treatment is going to cost me. Can we talk about it?
- Will my health insurance pay for this treatment? How much will I have to pay myself?
- I know this will be expensive. Where can I get an idea of the total cost of the treatment we've talked about?
- If I can't afford this treatment, are there others that might cost less but will work as well?
- Is there any way I can get help to pay for this treatment?
- Does my health insurance company need to preapprove or precertify any part of the treatment before I start?
- Where will I get treatment—in the hospital, your office, a clinic, or at home?

*Adapted from: American Cancer Society, 2017.*
cancer therapies continues to expand, incorporating next-generation targeted therapies and immunotherapy, clinicians must arm themselves with knowledge about the sources of financial toxicity of cancer treatment and the impact of this toxicity on our patients. In this setting, to stem the current tide of rising costs, clinicians must leverage this knowledge to move the policy discussion on costs of care forward and act now on access, affordability, and value in the use of these novel therapies.

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