DOI: 10.1002/cncr.34677

COMMENTARY

Incorporating financial toxicity considerations into clinical trial design to facilitate patient-centered decision-making in oncology

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Funding information
Susan G. Komen Foundation

Plain Language Summary

- Financial toxicity is increasingly being recognized as an important and devastating consequence of cancer treatment that receives little attention when clinical trials are being designed.
- There is a significant need to obtain this important information in an era of increasingly expensive anticancer treatments.
- Patients who are informed of all implications of therapy—efficacy, side effects, cost, and broader financial impact—are able to select the best cancer treatment for themselves.

Financial toxicity is increasingly being recognized as an important and devastating consequence of cancer treatment[1] that receives little attention in prospective clinical trial design. Its prevalence is high, ranging from 20% to 60% depending on the specific cancer studied.[2,3] In the past decade, we have learned much about financial toxicity. We can identify patients who may be at higher risk, including younger patients,[4] minoritized racial groups,[5] and patients in lower socioeconomic strata.[6] Financial toxicity can cause patients to skip doses or not fill prescriptions altogether.[7] Financial toxicity has a direct impact upon patients' quality of life,[8,9] puts them at risk for bankruptcy,[10,11] and may even increase mortality.[11] Methods to mitigate financial toxicity at the patient level exist but remain insufficient.[12]

Despite an understanding of the prevalence and consequences of this phenomenon, no robust mechanism exists to incorporate financial toxicity into patient-centered decision-making. Patients with cancer are often expected to decide between treatment options solely on the basis of efficacy or insurance coverage. These decisions rarely incorporate information on how treatment options affect patients' ability to return to work and generate the income to pay for basic necessities or continue providing for dependents. Our current framework of evaluation of cancer therapies, driven by clinical trials and sometimes postmarketing surveillance studies, does not prospectively obtain financial toxicity–related information to allow for incorporation of the potential financial impacts of treatment into risk/benefit discussions. A key barrier to fully informing patients is that clinical trials in the United States typically do not consider risk of financial toxicity when deciding what to test or what magnitude of benefit is needed to call a treatment beneficial.

This lack of ability to inform patients of expected impacts of therapies hinders truly informed decision-making for patients. As health care costs in the United States have risen exponentially,[13] the median cost of new cancer drugs has far outpaced the costs of other therapies[14] and is accompanied by rising out-of-pocket costs,[13] having a direct impact upon financial toxicity. These rising costs have not been accompanied by dramatic improvements in efficacy; rather, benefits of new therapies are stagnant or even decreasing as costs increase.[15] Drugs can now be approved through accelerated pathways at high costs to patients with modest improvements in intermediate end points, such as a 3%–4% absolute improvement in invasive disease–free survival (e.g., abemaciclib in hormone receptor–positive early breast cancer); an increasing number of drugs have been approved on the basis of high response rates (e.g., selpercatinib for non–small cell lung cancer [NSCLC]), again with an unclear impact on survival. Because trials typically do not collect information on financial toxicity, these benefits may not be appropriately contextualized to allow true understanding of the net benefit.

Oncologic clinical trials in the United States, mirroring broader trends in biomedical research funding more generally,[16] are largely

funded through industry,[17] where the drive to continue to improve cancer care also feeds off a potentially dueling interest of increasing profits. These competing interests can create perverse incentives where therapeutic options, particularly drug therapies, are tested in manners where the amount of drug used is maximized. Costly new adjuvant targeted therapies after surgery are commonly given for 1 year (e.g., ado-trastuzumab emtansine [T-DM1] in HER2-positive breast cancer) or 3 years (e.g., osimertinib in EGFR-mutated NSCLC). Efforts to identify appropriate dosing or administration length that accounts for the financial impact of treatment (on patients and the health care system) are lacking.

A common concept in oncologic drug development is the maximum tolerated dose, the highest dose a patient can tolerate without unacceptable toxicity, which is then further investigated for evidence of efficacy. We rarely think about identifying the minimal efficacious amount of a drug to minimize the financial impact of treatment.[18] Once positive trials identify a benefit to a particular therapy or dose of a drug, little incentive exists to perform another study to identify a minimally effective dose that might reduce the risk of financial toxicity. In fact, a perverse incentive exists against running additional trials that may show that less drug is needed, as the very entities that typically fund these studies would stand to lose money. De-escalation trials do exist, typically funded by government agencies, but have little support and myriad challenges.

A similar perverse incentive exists within radiation oncology, where long-course treatments have been favored as a result of radiobiologic concerns that were embedded into payment models connecting the number of treatments with remuneration. For example, the United States has been slow to accept shorter fractionation schemes for adjuvant radiation in early-stage breast cancer despite abundant evidence suggesting safety and efficacy. Moderate hypofractionation for breast cancer has had at least a 5-year follow-up since 2002, when a trial[19] reported noninferior oncologic outcomes after decreasing the length of radiation following breast-conserving surgery by 2 weeks. This was confirmed by additional trials in 2008[20,21] and became widely used in Europe. In 2010, hypofractionation use in the United States for breast cancer was <15%.[22] Consensus guidelines published in 2011[23] aided in increasing hypofractionation use, with approximately one third of patients receiving hypofractionation in the first 2 years[24] and two thirds of patients receiving hypofractionation 4 years after publication.[25] Nevertheless, within the United States fee-for-service remuneration model, financial loss from decreasing the number of treatments has been suggested to be a substantial barrier to wider adoption.[26]

Regardless of the oncologic data for hypofractionation in early breast cancer (suggesting good efficacy[19–21] and less toxicity[27]), the potential impact of fewer treatments on patients' financial well-being did not enter the discussion in consideration of adoption of hypofractionation prior to publications with a decade or more of follow-up data. A similar trend is playing out now for hypofractionation within prostate cancer.[28–30] Hypofractionation allows patients not to have to take additional weeks off work, pay for parking or gas,[31] or pay for child care for additional appointments and may impact other nonpaid caring roles. For some patients, this reduction in financial impact could outweigh uncertainties regarding longer term efficacy and help patients make appropriately individualized decisions.

The lack of consideration of financial impact is all the more concerning with increasing approval of oncologic drugs through accelerated approval pathways[32] rather than traditional pathways requiring clear impact on survival or other critical end points. Therapies that only show an impact on an intermediate end point should be subjected to full evaluation of their toxicities, and the risk/benefit discussion with patients should acknowledge both that a drug may have limited impact on standard end points (survival, quality of life) and that it may affect other end points such as financial toxicity. Data suggest that intermediate end points that lead to drug approval only rarely correlate with survival,[33,34] and many therapies (including changes in radiotherapy techniques) are adopted based on end points that do not correlate with survival, such as decreases in prostate-specific antigen blood levels.[35,36] Although many approved drugs later successfully complete confirmatory trials, a nontrivial minority of drugs approved via accelerated approval later fail on confirmatory trials (e.g., gefinitinib in unselected NSCLC, tositumomab in follicular lymphoma).[37] In the face of increasing costs of therapies,[14] which are likely to affect financial toxicity,[13] the full additional risks of novel therapies (including financial risk) should be balanced with the potentially lower clinical benefit when approvals are based on unproven end points.

The Food and Drug Administration (FDA) is currently undertaking a review of the accelerated approval program that bases drug approval on surrogate end points, which is expected to be completed in 2023.[38] This was prompted by the FDA's controversial approval of aducanumab (Aduhelm) for Alzheimer disease.[39] In the face of increasing risk of financial toxicity with rising drug prices[14] and out-of-pocket costs[40] combined with unclear clinical benefits,[15] the ongoing review of the accelerated approval pathway may offer an opportunity to consider the financial impact of therapy in all fields of medicine, and especially in fields such as oncology, where the impact of financial toxicity has been clearly demonstrated.

Within the development of both anticancer drugs and other therapies, consideration of the financial impact of treatment is essential when helping patients select their best options. Improving patient-centered decision-making to include financial toxicity may improve care for marginalized and underserved populations, impact those in low-/middle-income countries who look to the United States for guidance on best practices, and generate further work into advocacy and improving risk/benefit discussions.[41,42] Unfortunately, our current framework of evaluation of cancer therapies, driven by clinical trials, does not prospectively obtain financial toxicity–related information. A lack of prospective collection of these data precludes the ability to share this information with patients or incorporate it into formal evaluation of trial outcomes in a way that physical toxicity risk is measured and accounted for. Of course, information collected in clinical trials will necessarily be incomplete, particularly when investigating new drugs, where typically the cost of

investigational agents is borne by the study sponsor. Nevertheless, because not all financial toxicity derives from direct drug costs, clinical trials must collect information on the impact of different approaches on financial toxicity, which can develop when treatment-related toxicity causes differences in missed work, the need for domestic care resources, or additional travel for medical visits. A comprehensive framework for financial toxicity must include these indirect costs because such data are essential to complement information on the direct costs of the different regimens themselves. We must also collect information about the financial impact of treatments once translated into the real world, especially given that not all patients have the same out-of-pocket costs associated with any particular regimen, even when drug costs are not being entirely covered by a clinical trial sponsor.

It is also essential to expand efforts to improve the value of care. Small efforts to peel back the number or intensity of therapies in a manner that may reduce financial toxicity have taken place.[43–46] Retrospective data can create hypothesis-generating data such as whether shorter durations of adjuvant therapy may offer equivalent outcomes; for example, a recent study utilizing a Veterans Affairs population suggested that halving the length of adjuvant durvalumab after definitive chemoradiation for locally advanced NSCLC might maintain excellent outcomes,[43] which may deserve further investigation. Pharmacokinetic studies identifying optimal methods of drug delivery, termed "interventional pharmacoeconomics,"[47] may offer methods to test lower dosing of medications. Smaller studies have begun examining the financial implications of treatment (e.g., the single-institution study registered as NCT03506451). Partnership with insurance companies can result in initiatives aiming to improve quality,[44] such as promoting the use of hypofractionation, which decreases costs borne by insurers and patients alike. Novel payment methods that aim to remove fee-for-service remuneration may further change incentives that drive oncologic practices.[45,46]

Federally funded cooperative groups can run practice-changing clinical trials, free from the perverse incentives faced by industry payers that must maintain profits. Nevertheless, de-escalation studies are challenging, often requiring large numbers of patients to power noninferiority designs. Creative alternative approaches, including novel quantitative[48] or qualitative methods for determining noninferiority margins that could at least in theory include the disutility caused by financial toxicity or exploring single-arm cohort studies, merit consideration.

Cooperative groups have also begun examining the real-world financial impact of treatment in a manner that allows for the prospective collection of these data. For example, the Southwest Oncology Group's CREDIT study (NCT04960787) is examining the use of financial navigation to mitigate financial toxicity. ECOG-ACRIN recently completed a study assessing the financial impact of colorectal cancer treatment by utilizing the Comprehensive Score for Financial Toxicity (COST)[49] measure (NCT03516942). Integration of measures such as COST with other objective measures of financial impact of cancer treatments, such as out-of-pocket costs, into trial design may add critical information that will aid us in engaging in true shared decision-making with our patients. Requiring reporting of such information during drug approval, particularly accelerated approval based on surrogate end points, may further build the infrastructure needed to begin the prospective collection of financial toxicity data. This infrastructure will need to include prospective collection both in trials and in patients' real-world experiences.

Furthermore, as the health care system engages in such efforts to mitigate financial toxicity, a concerted effort to address the embedded racial and ethnic disparities experienced by patients with cancer is needed. Racial disparities in financial toxicity exist,[50] yet efforts to develop measures for financial toxicity outcomes and interventions (such as financial navigation) have not typically included a diverse cohort of patients representative of the racial and ethnic makeup within the United States. For example, the development of

TABLE 1 Summary of financial toxicity considerations in clinical trial design.

Timing	Ways to incorporate financial toxicity considerations
Clinical trials	• Fund de-escalation trials, including efforts identifying the minimal efficacious amount of drug needed or methods to increase the efficiency of care delivery to reduce burden and cost to patients • Support methodological techniques that optimize the ability to conduct de-escalation efforts, such as novel methods for determining noninferiority margins • Improve applicability of financial toxicity research by developing culturally sensitive measures to address inequities in financial toxicity risk • Collect prospective financial toxicity information including both direct costs (e.g., cost of drug, supportive care) and indirect costs (e.g., time off work, dependent care) during trial conduct using rigorous measures (e.g., COST,[49] ENRICh)
Postmarketing surveillance	• Police completion of confirmatory trials and withdrawal of indications when necessary • Require updating financial toxicity information collected in phase 3 with real-world information after drug or therapy approval • Incorporate collection of both direct and indirect costs in real-world settings • Encourage research into shared decision-making to identify optimal methods to incorporate financial considerations into the informed consent process

Abbreviations: COST, Comprehensive Score for Financial Toxicity; ENRICh, Economic Strain and Resilience in Cancer.

the COST measure utilized a patient population that was 74% non-Hispanic White[49] as compared to 58% within the broader United States population. Ongoing research is needed to determine optimal methods for measuring financial toxicity with a focus on developing culturally sensitive measures to improve access and equity for underserved populations who are most vulnerable to this adverse effect. Development of these measures will further supplement efforts to prospectively measure financial toxicity outcomes.

To manage the perverse incentives of industry-funded trials within our fee-for-service remuneration system and the need for ongoing clinical development, we should incorporate robust collection of financial toxicity outcomes and considerations of financial toxicity into clinical trial design and subsequent real-world evaluations, in order to allow for better understanding of the true net benefits of various treatment options and patient-centered decision-making (see Table 1). Although small improvements in surrogate end points may be worth anything for some patients, for others, pursuing marginal gains may impede paying for housing or returning to work. Patients who are informed of all implications of therapy—efficacy, side effects, cost, and financial impact—are best able to engage in decision-making.

AUTHOR CONTRIBUTIONS

Both authors have made substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work and to the drafting of the work or its critical revision for important intellectual content; have given final approval to the version to be published; and have agreed to be accountable for all aspects of the work to ensure that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

Reshma Jagsi's effort was supported by a Senior Scholar Grant from the Susan G. Komen Foundation.

CONFLICT OF INTEREST STATEMENT

Reshma Jagsi has received stock options as compensation for her advisory board role in Equity Quotient, a company that evaluates culture in health care companies. She has received personal fees from the National Institutes of Health as a special government employee (in her role as a member of the Advisory Committee on Research on Women's Health and the Board of Scientific Counselors), the Greenwall Foundation, and the Doris Duke Charitable Foundation. She has received grants for unrelated work from the National Institutes of Health, the Doris Duke Charitable Foundation, the Greenwall Foundation, the American Cancer Society, the Susan G. Komen Foundation, and Blue Cross Blue Shield of Michigan for the Michigan Radiation Oncology Quality Consortium. She has a contract to conduct an investigator-initiated study with Genentech. She has served as an expert witness for Sherinian and Hasso, Dressman Benzinger LaVelle, and Kleinbard LLC. She is an uncompensated member of the National Academies of Sciences, Engineering, and Medicine's Committee on Women in Science, Engineering, and Medicine. Laila A. Gharzai declares no conflicts of interest.

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