Reducing the toxicity of cancer therapy: recognizing needs, taking action

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Abstract | Our understanding of the biology of cancer and the application of this knowledge to cancer treatment has greatly outpaced what we know of the biology underlying the symptoms and toxic effects that therapies produce. These adverse effects of therapy cause substantial discomfort and distress to patients and their families, limit treatment tolerability and can persist indefinitely in post-treatment survivorship. Despite these concerns, little research effort is targeted at documenting the nature of these effects. Similarly, limited efforts are being made in the drug-development arena to identify or develop treatments that might prevent or reduce toxicities. A panel of clinicians and researchers as well as representatives from advocacy groups, federal agencies and the pharmaceutical industry was convened to identify gaps in cancer treatment toxicity research and to provide direction for future action. With an emphasis on coordinating multidisciplinary efforts, this panel has presented a strategy to increase funding for the field and develop a coherent research agenda.

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Introduction

Understandably, most cancer care and research is focused on curing the disease. This disease-directed focus on 'the cure' (or at least slowing cancer's progression) has resulted in a fundamental lack of appreciation by physicians for the significant toxicity and symptom burden observed with all forms of cancer therapy. The gap in our knowledge of the prevalence, severity and consequences of these toxic effects, as well as of their biological underpinnings, impedes progress in the identification and implementation of the research necessary to prevent or mitigate the adverse effects of cancer therapy. With the number of patients and survivors of cancer in the USA exceeding 12 million,[1] the extent, costs and mechanisms of these toxicities must be addressed by developing methods to treat or prevent them.

The adverse effects of cancer treatments can affect every part of the body. Major examples of these adverse events can be found in Table 1, although this list is far from exhaustive. Traditional chemotherapy and radiation therapy kill healthy cells as well as cancer cells and are known to be associated with systemic symptoms, such as nausea, fatigue and pain.[2] Targeted anticancer therapies—such as tyrosine kinase inhibitors (TKIs) that restrain dysregulated signalling pathways in cancer cells and hence the growth of cancer cells—are generally thought of as less toxic because of their specificity.[3] However, these agents often disrupt signalling pathways needed for normal cell growth and can elicit unique organ-specific toxicities.[4–8] Often, the extent of the toxicity burden is unknown until the drug is administered to a large population of 'real-world' patients with comorbidities that were not examined in a clinical trial, or until long-term follow up uncovers late-onset toxicities. In addition to specific adverse effects listed in Table 1, many cancer therapies can even cause secondary tumours.[9–13]

For most of the toxic effects caused by cancer treatment, no approved mitigating therapies or evidence-based management strategies are in place. Efforts to develop nontoxic cancer treatments or therapies to relieve treatment-related toxicities are hampered by a lack of mechanistic insight into these adverse events, the difficulty in objectively measuring treatment-related toxic effects and the lack of good preclinical models and assays by which to test potential therapies directed at toxicity reduction or prevention. Funding for symptom and toxicity research is limited, and uncertainty remains as to the will of regulators to accept symptom measurements.[14] These barriers have resulted in little systematic research being conducted in early-phase studies of toxicity management, or in the development of evidence-based toxicity-focused interventions. One exception is in the arena of reducing adverse effects of radiation therapy: increased interest in protecting citizens and soldiers from nuclear threats has spurred preclinical research into agents that mitigate radiation injury, some of which might be of use in oncology.[15] Furthermore, strategies to predict the risk associated with many specific cancer therapies, or those resulting from new agents, have not been developed.

Much to the benefit of patients, there has been increasing emphasis on incorporating principles of palliative care management earlier in the trajectory of cancer care, and practice guidelines have been developed for managing many of the toxicities of cancer therapy.[16] Unfortunately, most of these guidelines are based on consensus of best practice, with little evidence to support their implementation. Even with available management strategies for well-documented toxicities, patient care suffers from a lack of coordination among oncologists, other specialists and primary care providers.[17]

In March 2011, The University of Texas MD Anderson Cancer Center in Houston, TX, USA, partnered with Friends of Cancer Research, based in Washington, DC, USA, to host a colloquium in Houston entitled Developing Strategies for Reducing Cancer Treatment-Related Toxicities and

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Table 1 | Most common adverse effects of cancer therapy

Therapy	Associated effects	Examples
Surgery	Inflammation; anatomical complications or infection	Lymphoedema and pain[64] induced by abdominal surgery Loss of voice after neck surgery[65]
Radiotherapy	Damage to noncancerous tissue; other effects are site-dependent	Pneumonitis[66,67] induced by thoracic radiation Fatigue, cognitive dysfunction, mood disorder[68–70] induced by brain radiation Gastroenteritis (nausea, vomiting, diarrhoea, weight loss)[71] induced by abdominal radiation
Cytotoxic chemotherapy	Cell death in noncancerous cells; systemic effects include, but are not limited to, central and peripheral neurotoxicity, cardiotoxicity, gastrointestinal toxicity and immune suppression	Peripheral neuropathy[72–75] following taxane and platinum therapy Fatigue, cognitive dysfunction, depression[46,68,70,72] induced by chemotherapy Cardiomyocyte damage (irreversible; can lead to left ventricular dysfunction and heart failure)[76,77] induced by anthracycline Vascular complications (ischaemia, thrombosis)[78] induced by antimetabolites Gastroenteritis[71] induced by chemotherapy Neutropenia (leading to high risk of infection)[79] induced by chemotherapy
Hormone therapy	Disrupts endocrine system	Osteoporosis[80] induced by androgen-deprivation therapy and aromatase inhibitors Sexual dysfunction[81] induced by oestrogen therapy
Targeted therapy	Disrupts signalling pathways required for normal cell growth and function; other effects are pathway-dependent	Metabolic toxicities (hyperglycaemia, hypertriglyceridaemia, hypercholersterolaemia)[82] induced by mTOR inhibitors Dermatologic toxicity[4] induced by EGFR inhibitors Cardiovascular toxicity (hypertension, thrombosis, angioedema)[76,83] induced by tyrosine kinase inhibitors and angiogenesis inhibitors Immunosuppression[84] induced by B-cell therapy

Symptoms. The meeting was sponsored by the C. Stratton Hill Colloquium on Pain and Its Relief. The individuals approached to participate in the colloquium were identified by the sponsors and were believed to be high-level stakeholders who could best research, advocate for and effect policy change toward understanding, managing and possibly eradicating the negative consequences of cancer treatment. These stakeholders attended from universities, hospitals, government agencies and pharmaceutical companies: The University of Texas MD Anderson Cancer Center, Baylor College of Medicine, Texas Oncology, Memorial Sloan–Kettering Cancer Center, National Cancer Institute (NCI), FDA, American Cancer Society, ASCO, American Society for Therapeutic Radiation Oncology, National Comprehensive Cancer Network, Oncology Nursing Society Foundation, National Coalition for Cancer Survivorship, National Center for Policy Analysis, National Patient Advocate Foundation, American Association for Cancer Research Survivorship Task Force, Lance Armstrong Foundation, Duke University Medical Center, Amgen, Pfizer, Genentech and Novartis.

The stakeholders participated in working groups and panel discussions to identify the challenges that have prevented progress in reducing treatment-related toxicities and symptom burdens and to develop strategic steps to meet these challenges. Recommendations were identified in five key areas: increasing the recognition of the impact of treatment-related toxicities on patients; improving cancer care in the clinic; promoting symptom and toxicity research; establishing research needs and an agenda; and developing a policy and advocacy strategy. In this Perspectives article, we discuss each of these key areas and the ways to address the challenges faced in this important arena of oncology care.

Increasing recognition

A primary objective of the colloquium was to develop research strategies to determine the percentage of people affected by both acute and long-term toxic effects of cancer treatments as well as the severity of these adverse effects. Panellists recommended several strategies to identify the gaps in our current knowledge of treatment-related toxicities and to collect further toxicity epidemiology data once areas of need have been identified (Box 1).

The first step towards understanding the consequences of treatment-related toxic effects should be to conduct an inventory of symptoms and toxicities via a meta-analysis of the literature from clinical trials and observational studies. Most data about treatment-related toxic effects stem from industry-sponsored trials for regulatory approval, and generalization to the larger community of patients with cancer is problematic. The other major source of information about toxic effects is post-marketing reporting, which, in the USA, typically entails electronic submission of an adverse event to the FDA's Adverse Event Reporting System (AERS).[18] Adverse event reporting can facilitate the detection of rare treatment-related toxic effects; however, because reporting to AERS is voluntary and can be performed by anyone, there are risks of under-reporting as well as biased and duplicated reporting.[19]

Analysing the data from these heterogeneous reports to determine causality or the percentage of a population experiencing an adverse event is difficult. Thus, a major panel recommendation was to establish a system of active monitoring for acute toxic effects beyond clinical trials. A proposed FDA programme, the Sentinel Initiative,[20] seeks to monitor the safety of regulated drugs through a national, integrated, standardized electronic system with access to electronic health records and insurance claims. Data would be maintained by individual institutions (such as insurance companies) to protect patient privacy. An operations centre would run queries to each participating institution and aggregate the resulting de-identified data. Currently in the pilot stage, the Sentinel Initiative will initially be used only by the FDA, with the goal of detecting adverse effects more quickly than they are currently identified. However, an important limitation of this system is that it requires prospective determination of what outcomes should be monitored and how often (for example, active monitoring for signals of hypertension or arrhythmia in agents suspected to be cardiotoxic).

Panellists also suggested that toxicity data could be collected through the American College of Surgeons' Commission on Cancer National Cancer Database[21] and that networks of cancer-care providers, such as the US Oncology Network, could be tasked with collecting toxicity reports and longitudinal data on care provided to patients with cancer. Existing registries, such as the Surveillance, Epidemiology and End Results (SEER) programme[22] of the National Cancer Institute (NCI) and the Center for Disease Control and Prevention's National Program

of Cancer Registries,[23] could be enhanced to include toxicity and symptom data. SEER currently collects population-based incidence, prevalence and survival data from a subsample (28%) of the US population that is representative of the entire US population in terms of race, ethnicity and socioeconomic status.[22] Using existing registries and health-information technology could contribute to a rapid-learning health-care system that would improve our understanding of the epidemiology of toxicities and overall cancer care.[24]

The panel emphasized the need to develop mechanisms for long-term monitoring of patient experiences beyond the duration of typical clinical trials. Long-term outcomes data could be obtained through NCI cooperative groups, which are consortia of cancer centres, academic researchers and community oncologists who perform multi-institutional clinical trials to address pressing challenges in oncology, such as how to improve patient quality of life.[25] Panellists suggested that the efforts of these cooperative groups could be aligned with those of survivorship programmes. Also, longitudinal data could be collected through online patient advocacy communities. An example of such a community is PatientsLikeMe®, where patients share information on their disease, drugs or supplements they are taking and the response of their disease to those drugs as well as the adverse effects they experience.[26] One PatientsLikeMe® research team predicted the response of patients with amyotrophic lateral sclerosis to lithium carbonate treatment months before randomized trials reached the same conclusion,[27] highlighting the possible utility and power of such tools.

Finally, large prospective observational studies of long-term outcomes are needed. Many clinical trials follow patients for only a short duration after completion of treatment. Long-term studies must be adequately powered to determine if a post-treatment adverse event is in fact caused by the treatment. Panellists noted models for long-term follow-up studies, such as the Childhood Cancer Survivor Study[28] and the Alzheimer's Disease Neuroimaging Initiative (ADNI),[29] which provides a model for conducting multi-institutional studies that include comprehensive neuropsychological assessment, imaging, genetic analyses and biomarkers. An initiative like ADNI that examines several post-treatment toxicities could significantly advance our understanding of cancer treatment-related toxicity.

Box 1 | Recommendations for collecting toxicity epidemiology data

Synthesize existing information
- Search the literature for meta-analyses of large-scale observational studies

Use existing mechanisms to collect new information
- Monitor acute toxic effects through FDA Sentinel Initiative[20]
- Collect toxicity reports and longitudinal data from cancer-care providers
- Adapt existing registries to include toxicity and symptom data, such as the ACoS CoC national database[21] and NCI SEER registry[22]
- Include long-term outcomes data in NCI cooperative group research
- Enlist patient advocacy organizations to collect longitudinal data

Adapt existing models for prospective long-term observational studies
- Adapt Childhood Cancer Survivor Study[28] for long-term studies of adult survivors
- Use ADNI[29] as a model for collecting epidemiology data linked with genetic biomarker data

Abbreviations: ACoS CoC, American College of Surgeons' Commission on Cancer; ADNI, Alzheimer's Disease Neuroimaging Initiative; NCI, National Cancer Institute; SEER, Surveillance, Epidemiology and End Results.

Improving care in the clinic

Although our understanding of most treatment-related toxic effects and how to reduce these effects is lacking, some symptoms and toxicities can be addressed through proactive management in the clinic and integrating palliative care with disease-directed treatment. Educating health professionals, patients and their families as well as policymakers about treatment-related toxic effects and known management strategies is an action step we can immediately take to help reduce patient discomfort and improve patient and family quality of life.

A key panel recommendation in this area is to enhance physician training in multidisciplinary care to better equip primary care physicians, oncologists and other professionals with the skills they need to effectively assess and address pain, distress and other symptoms that burden patients and their families. Core competency training in palliative care and toxicity management should be required for all fellows and included across all disciplines—oncologic and nononcologic physicians should be trained to anticipate, recognize and manage medical toxicities and, in complex cases, should be encouraged to request specialized assistance. For example, organ-specific intervention, such as the involvement of a cardiologist in the event of heart failure or a pulmonologist in the event of lung injury, should be requested.

Panellists discussed the need for integration of known symptom management strategies and guidelines into clinical practice. For example, management strategies have been devised for the dermatologic toxicities of EGFR inhibitors[30] as well as for the metabolic disorders induced by treatment with mTOR inhibitors.[31] Additionally, evidence-based guidelines for standard clinical practice and, in some cases, for management of specific adverse effects of cancer treatments are published by organizations such as ASCO and the National Comprehensive Cancer Network (NCCN). For example, NCCN has guidelines for cancer-related pain,[32] antiemesis[33] and management of chemotherapy-induced anaemia.[34] ASCO also has guidelines for the use of antiemetics[35] and chemotherapy and radiotherapy protectants[36] as well as for prevention and management of venous thromboembolism.[37] However, even though these guidelines exist, compliance is not mandatory. Monitoring prescribing patterns and providing incentives for following established guidelines could help increase adherence to these guidelines.

Another recommendation in this area is to empower patients and their families by making them aware of the availability of multidisciplinary care teams who can work with a patient's primary doctor to provide an extra layer of support in managing symptoms, pain and stress. Patient and family goals should be identified early in the disease course and every discussion about a potential therapy option should include information about the possible toxicities of that treatment and any known strategies to mitigate those toxicities. Patient education could greatly improve the medical decision-making process and help patients manage their own symptoms. Educational activities should also be directed toward the patient's family and caregivers, as well as toward the internist participating in their care.

Promoting toxicity research

Research into the effects of treatment-related symptoms on patient outcome has been hampered by funding issues and the low priority given to the development of new agents for toxicity management. Although the area of palliative care is an increasingly

Box 2 | Recommendations for increased funding and visibility of toxicity research

Develop a focus on cancer treatment toxicities at the NIH
- Create an office within the National Cancer Institute dedicated to toxicity research
- Integrate toxicity research across all NIH institutes

Incorporate symptom and toxicity expertise into NIH study sections
- Incorporate clinicians, clinical trialists and basic scientists familiar with cancer treatment toxicities into existing study sections, namely Clinical Oncology, Developmental Therapeutics, Radiation Therapeutics and Biology
- Create new study sections to focus on basic and translational toxicity research

Identify new funding streams
- Develop partnerships to enable collaborations between the private and public sectors

Increase visibility of the results of toxicity research
- Incorporate symptom and toxicity expertise into mainstream journal peer review
- Dedicate visible toxicity symposia at major professional meetings

attractive field for those who treat patients,[16,38] toxicity-focused research is rarely chosen as a research career path in any oncology discipline. Also, such research is difficult to publish because there are few expert reviewers familiar with this topic, and, perhaps consequently, mainstream journals with the most impact in the field are wary of publishing the reports. Nonetheless, research into cancer therapy-induced toxicity could be quite productive, given the prevalence of many adverse effects and the opportunity they offer of studying a pathological phenomenon caused by a defined insult. Importantly, the panel agreed that generalization of potential findings in this area could extend beyond cancer care. If we brought to bear all of our tools for interrogating human physiology and pathophysiology, including our expanding knowledge of the human genome, epigenome and proteome, we could potentially improve our understanding of these toxic effects and develop effective interventions.

The panellists developed a set of recommendations to stimulate research in the USA into treatment-related toxic effects and to disseminate the results of such research (Box 2). Although the panel acknowledged that palliative care is often emphasized in European, Canadian and Australian cancer research agendas, precise information was not available about the level of toxicity research in these programmes. However, a recent report of the UK National Cancer Research Institute research priorities stated that investment in palliative and supportive care research amounted to <4% of all cancer research investment.[39] Personal communications with officials at the NIH suggest that the level of investment is lower in the USA.

A priority recommendation of the panel in this area was to develop an NIH–NCI structure for toxicity-related research. Although toxicity research implicates multiple NIH institutes and centres, the disease-focused mission of the NIH largely overlooks the issue of therapy-related toxic effects. Panellists suggested that an office should be created within the NCI specifically focused on studying the adverse effects associated with cancer treatments. Indeed, the Community Clinical Oncology Program within the NCI currently funds community-based symptom-management research, but this programme does not focus on mechanism-based toxicity research.[40] Furthermore, the NCI Office of Survivorship,[41] which supports research aimed at examining and controlling late effects of cancer treatments, is not focused on promoting and supporting research to elucidate the underlying biological mechanisms of treatment-related toxicities. Importantly, the focus on cancer treatment-related toxicity should not end with the NCI. Toxicity research should be integrated across all NIH institutes, and interactions between the NCI and other NIH departments should be encouraged to promote multidisciplinary science. For example, a group studying chemotherapy-induced neuropathy should include not only oncologists, but also experts in neuroscience.

The panel agreed that the NIH and NCI must develop granting mechanisms that encourage toxicity research. Most importantly, study sections reviewing grants for toxicity research must have the relevant expertise. The panel suggested that such expertise be incorporated into existing study sections, or that new study sections be formed to focus on basic and translational toxicity research. Specifically, the panel identified three existing study sections that would benefit from the inclusion of clinicians and clinical trialists familiar with cancer treatments and the toxicities they cause: Radiation Therapeutics and Biology, Developmental Therapeutics and Clinical Oncology. Although these sections focus on new therapeutic agents, they could also review studies aimed at understanding the toxicities of agents currently in use. One mechanism to promote participation would be to include toxicity research as a target of the Clinical and Translational Science Awards.

Funding for toxicity-related research is desperately needed and this should be a priority of the NIH. Panellists noted, however, that the current fiscal environment requires that new funding streams be identified. This area is ripe for the involvement of public–private partnerships to enable collaboration between the NIH or FDA as well as stakeholders in the private sector, such as pharmaceutical companies or patient-advocacy organizations such as the American Cancer Society, Lance Armstrong Foundation, Susan G. Komen for the Cure and the Leukemia and Lymphoma Society. The Foundation for the NIH, for example, has convened projects with a variety of stakeholders that support a deeper understanding of drug safety. These projects include the Drug-Induced Liver Injury Network, which is focused on liver injury caused by prescription and nonprescription drugs,[42] and the Observational Medical Outcomes Partnership, which researches methods to analyse healthcare databases for the identification and evaluation of safety signals from prescribed drugs.[43] More projects such as these, with a focus on cancer treatment-related toxicities, are needed.

In addition to finding funds for toxicity research, mechanisms must be developed to increase the reporting of the results of symptom and toxicity research and the visibility of that reporting. As with grant review, peer review at mainstream journals must include symptom and toxicity expertise. The panellists also agreed that professional organizations, such as ASCO, the Oncology Nursing Society, American Association for Cancer Research, American Society for Therapeutic Radiology and Oncology and American Society of Hematology, should dedicate visible symposia and poster sessions at their professional meetings. Highlighting toxicity research can promote the field to young researchers in basic, translational or clinical science as a possible career choice. Training and workforce development programmes should be developed using NIH training awards to further incentivize toxicity research.

Establishing a research agenda

In addition to active and long-term monitoring of toxic effects, the panellists agreed that the most pressing basic and translational research needs are related to laying the 'groundwork' for developing new drugs to prevent or mitigate toxic effects. Research should focus on tailoring curative treatments with consideration for toxicity risk, and on preventing and controlling adverse effects. These research areas encompass the development of better screening or preclinical methods to detect toxic effects before a therapeutic candidate goes to trial, mechanism-of-action studies to determine how certain toxic effects become manifest and the development of predictive and surrogate genetic and proteomic biomarkers to identify patients at high risk of having adverse effects (Box 3).

Box 3 | Recommendations for toxicity research agenda

Develop preclinical models of treatment toxicities
- Animal models for mechanism-of-action studies
- Cellular assays for high-throughput screening of new drug candidates to detect toxicities early in development

Use systems-biology approaches in toxicity research
- Correlate clinical adverse events to predictive biomarkers
- Identify signalling pathways involved in treatment-induced toxicities

Collect symptom data in clinical trials
- Collect rigorous PRO data
- Use existing PRO measurements
- Develop and validate new PRO measurements
- Develop new and use existing standardized quantitative measures of toxicities
- Seek FDA guidance early in development to ensure adequate symptom measurement

Abbreviation: PRO, patient-reported outcome.

Preclinical toxicity studies of anticancer agents are usually designed to detect severe damage to vital organs.[44] Many of these do not correlate well with toxicities in humans and cannot be used for mechanistic studies or for the evaluation of potentially mitigating therapies.[45] However, a few preclinical animal models of major toxic effects (for example, models of therapy-related cognitive dysfunction[46] or mucositis[47]) are available, although limited effort has been made to use these models for mechanistic studies. The development of animal models for treatment-related fatigue, disrupted sleep, motivational loss and cognitive deficit is currently an active area of research and might provide a better mechanistic understanding of why treatment produces these symptoms.[48,49] Indeed, matching of patient symptom reports to murine behaviour is possible, albeit difficult, and these efforts are guided in part by patients. In addition, mouse models of pneumonia have been developed to study the mechanism of chemotherapy-induced pneumonia in patients with leukaemia and to test potential mitigating therapies.[50] Several mouse models have also been developed to study the mechanism of cardiotoxicity related to TKIs and to determine ways to predict patients at risk of cardiotoxicity.[51] Rat models of neuropathy have also been developed.[52] Despite these advances, additional animal models are needed for preclinical mechanism-of-action studies and for screening strategies that incorporate assessment of toxicity to vital organs (the kidneys, liver, brain, heart and peripheral nervous system).

Another priority is the development of simple cellular assays that are amenable to high-throughput screening and yield a readout that is both sensitive and specific for clinically significant, dose-limiting toxicities. In addition to providing information about the toxicities of new anticancer agents that will eventually become approved for use in patients, such a screening strategy could potentially reduce the number of early-phase trials of agents that ultimately fail because of drug intolerance and reduce the significant costs of these trials to the biopharmaceutical industry. The cell types used would depend on the toxicity being studied, and care would be needed to ensure that the most relevant cell type is chosen for preclinical studies. For example, human embryonic stem-cell-derived cardiomyocytes might be of use in screening agents for cardiotoxicity and far more relevant than performing such screening assays in cardiomyocytes derived from rodent sources.[53]

Systems-biology approaches could provide predictive and mechanistic insight and facilitate the identification of relevant biomarkers.[54] Indeed, systems-biology has become a priority focus at the FDA Center for Drug Evaluation and Research, as evidenced by its new pharmacological mechanism-based drug safety assessment and prediction programme,[55] which will provide hypothesis-generating data to complement pharmacovigilance surveillance programmes. As a part of this program, the FDA (in collaboration with Friends of Cancer Research, Reagan–Udall Foundation and Susan G. Komen for the Cure) has initiated a pilot project using a systems-toxicology approach to evaluate the mechanisms of cardiotoxicity of TKIs.[56] Using data mined from both published literature and secondary safety analyses from clinical trials, the project aims to determine patterns of cardiotoxicity elicited by different TKIs, which will then be correlated with genomic and proteomic analyses in a selection of preclinical models of cardiotoxicity. The ultimate goals of this project are to determine how well various preclinical models correlate with clinical adverse events and to identify biomarkers of cardiotoxicity that can be screened early in the drug development pipeline. Ideally, results from this project will guide future, similar studies of other toxic effects.

In clinical studies, sponsors should collect rigorous data on the toxicities of new drugs from the patients' perspectives, in addition to the routine reports of adverse events, which typically stop after approximately 3 months. Sponsors in oncology drug development must prioritize the inclusion of patient-reported outcomes (PROs), which are patient ratings of the severity of adverse effects and symptoms, in their development plans. PROs should also include health-related quality of life and health-economic data. To improve the existing PRO infrastructure, the refinement of existing PRO measures as well as the development and validation of new PRO measures are needed. One initiative in this area is the effort of the NCI to include PROs in its Common Terminology Criteria for Adverse Events, which is the standard form that clinicians use to report toxicities of oncologic drugs.[57] Electronic methods of PRO data capture, such as computer–telephone interfaces or online reporting, greatly enhance our ability to capture such data routinely and to detect early signals of toxicity.[58] Aside from PROs, the development of standardized quantitative clinical measures of toxicities and the use of these measures in clinical studies is also required to understand the adverse effect of oncology drugs, especially new products. New or improved technology, such as advanced imaging methods, could also be used to examine both central and peripheral responses to toxic therapies.

Clear and consistent regulatory advice from the FDA might encourage sponsors to prioritize measures of symptoms and toxic effects as primary or key secondary end points in drug development plans. The FDA has signalled its interest in understanding the safety of oncologic drugs by restructuring its Oncology Office and creating the Division of Hematology Oncology Toxicology, which will be dedicated to reviewing nonclinical pharmacology and toxicology aspects of cancer therapies. Another indication of the FDA's commitment to understanding the adverse effects of cancer therapy is the 2009 publication of its guidance for industry on PROs, which specifies that experiences perceived by the patients (such as symptoms) are best measured using PROs.[59] The guidance for industry also outlines the methodological standards the FDA requires when using PROs to support labelling claims.[59]

Finally, in the post-marketing setting, observational studies such as registries and retrospective database analyses, which might include PROs and tissue or DNA collection, can help to generalize drug effects from clinical trials to the clinic. Additionally, tissue and DNA databases in particular might be useful in elucidating the mechanisms of disease as well as the safety of and response to therapy. A collaborative approach among the pharmaceutical industry, academia and clinicians is essential to support both preclinical and clinical investigator-initiated research.

Developing policy and advocacy

To convince policymakers to increase focus and funding on toxicity research and improving symptom management, the cost-effectiveness of reducing adverse effects of therapy must be demonstrated. Determining the consequences of toxic effects caused by cancer treatments on the health-care system will be necessary. How often do the unmanaged toxic effects lead to emergency room visits and hospital admissions? How much do these admissions cost the system? What is the cost in terms of lost work or productivity to the patients and their caregivers? Can toxicity management and supportive care be integrated into standard care to reduce the rate of early termination of effective anticancer regimens? Along these lines, can comprehensive cancer care (including proactive symptom management, toxicity management and other aspects of palliative care) reduce these burdens on the health care system?

Patients and health professionals must join forces to convince the scientific community, philanthropic funders and policy makers that toxicity research and symptom relief has value as an essential aspect of patient-centred care. Scientific and clinical communities need to advocate for changes in their own institutions to make toxicity research a priority. New researchers should be encouraged to take on toxicity reduction as an active area of investigation. Additionally, scientists in oncology need to reach out to professional organizations outside of oncology, such as the Endocrine Society, American College of Cardiology, American Heart Association, and others, to urge that they incorporate toxicity research and symptom management into their own agendas to promote the field as a valid arena for study.

Conclusions

That toxicity from cancer therapy can be debilitating, interfere with treatment dose and adherence, affect survival and persist indefinitely in cancer survivors is widely recognized by the oncology community. Much of the scientific expertise, from genomic or molecular to epidemiological and drug development, is already mature enough for rapid progress to be made in the reduction or prevention of treatment-related toxicities. The predominant need now is to recognize and quantify the consequences that these toxic effects have on patient function and survival as well as understand the individual and societal burdens that they cause. The next step is to develop a scientific strategy to coordinate the many disciplines that must work together to reduce adverse effects to therapy experienced. Variability in symptom and toxicity expression must be addressed; why do some patients have relatively minor toxic or symptomatic responses to cancer therapy, whereas the toxic effects of therapy can debilitate others with the same cancer who are undergoing the same treatment? The same methods being successfully used to understand the biological variability underlying risk for developing cancer, drug response and drug resistance could and should be applied to risk for toxicity. And, as we discover agents that modify drug resistance and the mechanisms that produce it,[60–62] the same discovery pathways should be applicable to toxicity reduction. An immediate need is the development of toxicity 'phenotypes', which will require refinement of toxicity measurement, both in the clinic and through behavioural and self-reported measures. Once these phenotypes gain consensus support, the research strategy will become more tractable to the cancer research community, and research approaches will become clearer. Work groups could be formed to focus on specific toxicities or clusters of toxicities that commonly co-occur—a strategy that has been productive with other health problems, such as rheumatic disease.[63] Early successes should sustain persistent efforts in this area.

Finally, advocacy from patient organizations and other groups who promote various areas of oncology research must be developed. Broad communication is essential to promote the message that the cost of developing this research (from training toxicity-focused researchers to expenditures for the wide range of research that is needed) is feasible, within our grasp and worth our efforts.

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Author contributions

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