Cancer treatments should benefit patients: a common-sense revolution in oncology

Many newly approved cancer therapeutics offer limited clinical benefits yet are still prescribed to patients. A common-sense revolution in oncology would prioritize treatments that meaningfully improve survival and quality of life.

Bishal Gyawali and Christopher M. Booth

Oncology needs a common-sense revolution. Although there has been important progress in some elements of cancer care, the cancer field is losing sight of what matters to patients. Hype has overshadowed hope, and biological plausibility precedes efficacy. The cancer community celebrates so-called 'game-changing' treatments on the basis of single-arm studies, observational data and even animal models. Even when randomized controlled trials (RCTs) provide evidence in support of treatment efficacy, there are many problems with such studies, including the promotion of statistical significance over clinical significance, the use of substandard control arms and subgroup analyses to claim treatment benefits, the use of non-inferiority design instead of superiority design, and the promotion of efficacy on the basis of surrogate or secondary endpoints[1]. These problems call for a common-sense revolution that will require paradigm shifts in education, research design and the delivery of cancer care (Table 1).

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Medical education

Many problems in oncology could be mitigated by the education of trainees, patients, the media and journal editors. Problems with oncology education, and potential solutions, are presented in Table 1.

The main challenge in education is the hype that surrounds new cancer therapies. The ability to critically evaluate the literature is one of the most important skills in clinical care; this should be emphasized in training programs and continuing education.

There is a prevailing narrative that all new treatments have a major clinical impact, which influences how physicians, lay people, policy-makers and politicians perceive these treatments. Health journalists have a role in this, as news stories of supposed treatment breakthroughs drive unrealistic patient expectations and pressure policy-makers to approve marginal treatments[2]. The reality is very different, as most advances in oncology are small and incremental.

Trainees need to be taught how to engage in difficult discussions about stopping anti-cancer therapy, rather than following the easier route of prescribing a marginal or ineffective drug. Journalists should be equipped with basic skills in critical appraisal that would allow them to ask tough questions and view press releases with skepticism and clarity. Oncology researchers should also recognize that in most cases, the main source of hype is their own community. The opening press conferences at annual meetings are often rife with hype surrounding 'major advances', but these advances are often modest.

Patients should be better informed and should be given unbiased educational materials that clearly explain magnitude of benefit, toxicity and cost. Social media is a major platform for oncology education of patients and others, but the content is not subject to critical review and is prone to spin

Table 1 | Current problems and potential solutions in oncology education, research and policy, and delivery of care

Domain	Problem	Potential solution
Education	Critical appraisal skills are lacking in oncology practitioners.	Include more evidence-based medicine and critical thinking in oncology training.
	Continuing medical education programs propagate hype.	Have an academic detailing model in which independent not-for-profit organizations run continuing medical education.
	Patients accept low-value care.	Have an independent organization, such as an academic center for sense in oncology, provide education to patients about evidence-based medicine, value-assessment tools and endpoints.
	Media overblows results from studies, contributing to hype.	Have an independent organization launch training programs for journalists on principles of evidence-based medicine and critical appraisal. Investigators and professional societies must not exaggerate their results in press releases.
	Poor-quality research influences practice.	Editors of medical journals should ensure that reported research is free of hype and bias. Conflicts of interests among editorialists must be minimized (i.e., not just disclosed). Institutional review boards and funding agencies should not facilitate low-value and poorly designed clinical trials.
Research and policy	Clinical trials do not serve patients and are designed to detect marginal differences in surrogate measures.	Patients must be involved in trial design, and potential participants must be educated about the characteristics (and potential pitfalls) of such trials. A major re-investment in cooperative groups is necessary to ensure that they (rather than industry) can lead the clinical-trials agenda with patient-centric research.
	Moonshot interventions get more funding than groundshot interventions.	Distribution of cancer research funding should be changed.
	Drug-approval standards have fallen.	Enforce the legal mandate for post-approval trials for drugs that receive conditional approvals; get patient input into trial design and prioritize clinical benefit over *P* value for drug approvals.
	Clinical guidelines may be biased.	Ensure the authors of guidelines are free of conflict of interest with the pharmaceutical industry. Include patients in guideline committees.
	Cancer drug prices are not sustainable.	Require value-based pricing in the registration of new drugs.
	Industry lobbyists exert undue influence on cancer policy.	Legislators and the public need to re-consider how this influence can be mitigated.
Delivery of care	Patients receive cancer treatment until the very end of life.	Encourage and formally teach end-of-life discussions.
	Physicians prescribe marginal low-value treatments.	Implement and extend 'avoiding wisely' or 'choosing wisely' campaigns.
	Drugs with minimal gains but substantial risks and costs are prescribed.	Present patients with better information about the benefit and harms of treatment, including costs. Provide oncology fellows training in health economics.

and bias. Consumers of social media should undertake their own critical appraisal of the evidence or ensure that they follow trusted and unbiased sources of online information. Patient-advocacy groups have an important role in producing educational materials, but many are funded by the pharmaceutical industry, which is a conflict of interest[3]. Similarly, medical journals, the gatekeepers of research, allow professional medical writers to author clinical-trial reports. This is a fairly new phenomenon and runs counter to many principles of academia; its potential impact on the interpretation of study results needs careful consideration[4]. Journals also invite editorials from authors with direct financial conflicts of interest with the same company whose product is being discussed, potentially leading to unduly favorable interpretation of trial results[5].

Clinical research

There are multiple threats to evidence-based oncology. Oncology invests heavily in poorly designed studies with endpoints that do not represent benefit to patients. Large trials are powered to detect differences in outcomes that are statistically, but not clinically, meaningful[6,7], with many treatments offering very small gains in survival. Because patient resources are finite, enrolling patients in these trials will have an opportunity cost by limiting the ability to conduct other trials that may answer questions that matter to patients. Trials that poorly serve patients are outlined in Table 2.

Cancer-research efforts are currently heavily directed by aspirational 'moonshot' initiatives; re-calibration is needed to also support low-tech inexpensive 'groundshot' interventions that can improve outcomes for many patients in the short term[8]. Research programs in quality of care and health-system performance need to be prioritized, and the funding portfolio needs to be re-balanced. A major challenge is that almost all oncology RCTs are funded by the pharmaceutical industry[4], which does not have an incentive to fund trials of inexpensive therapies or strategies.

Funding agencies and governments should support trials of interventions that can directly address common gaps in knowledge, influence delivery of care and address financial toxicity, including treatment de-escalation strategies. Low-and-middle income countries should prioritize trials that address cancers that are relevant in the local context and test interventions that could feasibly be implemented in a lower-resource setting[9]. Examples of cancer groundshot-type trials include the following: testing the role of primary tumor resection in metastatic cancer; testing the non-inferiority of a shorter duration of adjuvant therapies; and testing drug repurposing in solid tumors[9]. Results of such trials could immediately change practice in all health systems regardless of economic status.

Trials of new drugs should test endpoints that matter to patients: overall survival, and quality of life. Endpoints such as disease-free survival and progression-free survival should be used only if they have been shown to be valid surrogates for

Table 2 | Threats to evidence-based medicine in oncology

Threat	Examples
Abandonment of RCTs	- Approving drugs on the basis of single-arm trials
	- Using observational data (real-world evidence) as a replacement for RCTs
Inferior control arm in RCTs	- Using an outdated control arm regimen that has already been proven to be inferior in earlier trials
	- Using a placebo control where active treatment is the default standard of care
Surrogate markers as primary endpoints	- Using unvalidated surrogate endpoints such as progression-free survival or response rates
Overly narrow eligibility criteria	- Patients in trials are not representative of the general population
	- Overly strict eligibility criteria in RCTs leads to efficacy–effectiveness gap
Unjustified non-inferiority trials	- Using non-inferiority design trials without justification
	- Lenient definitions of non-inferiority
Inappropriate use of crossover design	- Prohibiting crossover design in tests of a drug in a first line that is already approved for later lines
	- Including crossover design in tests of a drug in a first line that is not yet proven in any setting
Substandard post-protocol therapies	- If patients do not get appropriate treatment after the protocol, those differences (rather than the trial intervention) can lead to survival changes
Informative censoring	- Patients may drop out due to side effects or lack of treatment efficacy; this will lead to over-statement of progression-free survival
Subgroup analysis	- Post-hoc and unpowered subgroup analyses can lead to false-positive results
Undermining toxicities	- Using terms such as 'manageable' or 'tolerable' to describe toxicities
Publication bias	- Not publishing or delayed publication of negative trials
Conflicted journal articles	- Trial reports authored by professional medical writers who are employed by the pharmaceutical company
	- Editorials written by experts with financial conflicts of interest

overall survival and quality of life. The oncology community needs to become more efficient in conducting research by running multi-center phase 3 RCTs instead of individual trials at separate academic centers. Multi-center trials can be managed by an independent agency, with analysis and reporting by investigators who are independent of the sponsoring company.

There should be a renewed investment in cooperative trial groups, which use public funds to lead trials that prioritize meaningful gains for patients. This will ensure a research portfolio that better balances industry trials led by contract research organizations.

Regulatory approval

An increasing number of cancer therapies receive conditional accelerated approval, which is based on non-comparative trials and surrogate endpoints. There have also been increasing voices promoting the use of real-world evidence to support drug approval. Although real-world evidence can address important questions in the delivery of cancer care, its use in showing the efficacy of new cancer therapies can be limited by methodological bias[10,11]. Accelerated approval comes with a mandate to subsequently test drugs in an RCT with appropriate clinical endpoints. This should be enforced by withdrawal of approval if confirmatory trials fail to show benefit[12]. Unfortunately, this is not currently the case. Despite negative confirmatory trials, in 2021, four of six drugs with accelerated approval were voted to stay on the market by the Oncology Drug Advisory Committee of the US Food and Drug Administration[12]. Many of these costly drugs offer very small benefits to patients[6]. Patient input should be obtained at every step of anti-cancer drug development, from trial design and trial interpretation to the writing of guidelines for new therapeutics[13].

Avoiding wisely

Too often in oncology, the harms of anti-cancer drugs are downplayed while the benefits are exaggerated[14]. An 'avoiding wisely' campaign would curtail the use of interventions that provide minimal or marginal benefits and may harm patients, instead offering patients a quality transition toward the end of life[15]. This will require better communication around prognosis, treatment intent and therapeutic benefit. Many patients undergoing palliative chemotherapy to prolong their life do not understand that the treatment will not cure them[16]. Most patients with advanced cancer overestimate the potential clinical benefits of treatment (as do their physicians[14]) and thus accept treatments with minimal gains[17].

Oncologists should also consider a patient's time when prescribing palliative chemotherapy, as time is especially important near the end of life[18]. Time spent pursuing small benefits of palliative regimens may represent an important opportunity cost, as patients lose time they could otherwise spend fishing, traveling and visiting loved ones.

Professional bodies

Medical oncology societies are in an ideal position to implement this proposed common-sense revolution. Societies for oncology professionals can provide easily accessible, bias-free oncology education globally, putting the patients first and reducing the influence of industry in continuing medical education and oncology guidelines. The adoption of 'Choosing Wisely' by the American Society for Clinical Oncology[19], the Value Framework of the American Society for Clinical Oncology[20], and the Magnitude of Clinical Benefit Scale from the European Society for Medical Oncology[21] are examples of important initiatives in this context. Together with professional societies, clinicians and investigators can advocate for these common-sense initiatives as the field moves toward a system that seeks to deliver meaningful care to all patients with cancer. ❐

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Reimagining patient-centric cancer clinical trials: a multi-stakeholder international coalition

The Bloomberg New Economy International Cancer Coalition brings together academia, industry, government, patient advocacy and policy think tanks to leverage technology and collaboration to improve patient access to clinical trials and to harmonize regulations aiming to accelerate cancer cures and prevention worldwide in the post-pandemic era.

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The COVID-19 pandemic upended the infrastructure and delivery of oncology clinical trials worldwide. In an effort to allow potentially lifesaving experimental therapies for patients to continue during the pandemic, government regulators, medical centers and clinical trial sponsors implemented unprecedented flexibilities in the conduct of clinical trials[1]. The US Food and Drug Administration (FDA), along with regulatory agencies from China, Russia, the European Union, Brazil, Australia and Nigeria, separately issued guidance that was adopted in their respective regions (Table 1). These measures provided new opportunities to optimize the patient experience and illuminated how digital technology and collaboration may improve access, alleviate patient burden and increase the diversity of participants, including those in remote and disadvantaged communities. To convert these improvements into a permanent paradigm change after the pandemic, a coordinated, global multi-stakeholder effort is required. In the spring of 2021, Bloomberg New Economy, Bloomberg LP's media and event platform tasked with advancing solutions to shared global challenges, launched the Bloomberg New Economy International Cancer Coalition. This initiative emerged from discussions on East–West collaboration between global leaders and experts at the 2019 Bloomberg New Economy Forum in Beijing. The Coalition gathered leaders from academic medical centers, government regulatory agencies, the pharmaceutical and biotechnology industry, contract research organizations, patient advocacy groups and policy think tanks to identify barriers and solutions that their respective institutions may cohesively act upon for worldwide impact (Table 2). The members of the Coalition have been convening regularly since July 2021 to explore ways to achieve better access to clinical trials and regulatory harmonization that will accelerate the development of novel cancer treatments, screening and prevention. The priorities of the Coalition were determined by means of an electronic voting system during the convening. The top three proposed actions that received the highest vote counts in each of three categories — patient identification and enrolment, treatment and monitoring, regulatory harmonization — were carried forward as recommendations.

Patient-centric clinical trials: expanding access to clinical trials beyond conventional trial sites

Patient-centric trials are defined as investigations that prioritize the needs of the patient at all stages, including design, activation, enrollment, data collection, completion and outcome reporting. In patient-centric trials, hypotheses that are important to patients can be formulated, study designs that minimize burden to patients can be employed, and measures that ensure that trial conduct and data generation are regulatory compliant and support potential improvement to the standard of care can be implemented. Technologies such as telemedicine and remote monitoring that were necessitated during COVID-19 pandemic lockdowns may become more broadly used for clinical trials in the future. There is now an opportunity to leverage cross-border regulatory efforts to harmonize the standards for conducting patient-centric