

REDEFINING CANCER: A NEW PARADIGM FOR BETTER AND FASTER TREATMENT INNOVATION

David J Stewart¹, Gerald Batist²

¹The Ottawa Hospital, University of Ottawa; ² Jewish General Hospital and Segal Cancer Centre, McGill University, Montreal

Corresponding Author: dstewart@toh.on.ca

ABSTRACT

Common cancers may arise from several different mutations, and each causative mutation may require different treatment approaches. There are also several mechanisms by which malignancies may become resistant to therapy, and each mechanism will also require a different therapeutic strategy. Hence, the paradigm of devising therapies based on tumor type is suboptimal. Each common malignancy may now be regarded as a collection of morphologically similar but molecularly distinct orphan diseases, each requiring unique approaches. Current strategies that employ randomized clinical trials (RCTs) in unselected patients carry a high risk of misleading results. Available data suggest that it is reasonable to grant marketing approval for new anticancer agents based solely on high single-agent response rates in small phase I-II studies involving molecularly-defined patient groups where benefit from other therapies is unlikely. This could markedly speed patient access to important therapies while reducing health care costs by slashing drug development costs. Feasible post-approval surveillance procedures could provide ongoing monitoring of drug safety. While assessment of drug combinations would be more complex due to variable contributions of each component, new strategies have been proposed. In addition to savings from more efficient clinical trials methods, it is essential that we also markedly reduce costs of complying with clinical research regulations. Compliance is too cumbersome and expensive, and current regulatory inflexibility markedly slows progress while escalating health care costs. This requires urgent attention. Regulatory approaches intended to enhance safety may instead potentially cost far more life-years than they save by delaying approval of effective therapies.

Key Words: *Cancer treatment, resistance, orphan drugs, innovation, clinical trials, genomic variation*

BACKGROUND

Knowledge about disease processes is progressing rapidly. However, our clinical research methodologies and treatment approval approaches often impede translation of this knowledge into effective new therapies.¹⁻³ Randomized clinical trials (RCTs) (our gold standard for defining whether new therapies add benefit) have serious limitations.³ Most RCTs assess an otherwise unselected population of patients sharing a morphologic diagnosis (eg, breast cancer) and primarily address whether there is a therapeutic effect in the “average” patient. Lack of statistical significance may lead to discarding therapies that

are nevertheless of marked benefit in small subpopulations. Conversely, even if the therapy only works in a small subpopulation, it may have a great enough impact that statistical significance is achieved. If it is not recognized that benefit is confined to a subpopulation, the therapy may then be used in the entire unselected patient population, including patients in whom it cannot work, thereby increasing health care costs, decreasing therapy cost-effectiveness, exposing patients to the toxicity of therapies that cannot help them, and delaying patient access to therapies that might actually work for them.³ Given this emerging portrait of current drug development, questions

arise about the merit and even the ethical basis for continuing with the status quo.¹⁻³

To optimize statistical power, RCTs typically accrue large patient numbers. The requirement for large patient numbers substantially increases the amount of time required to complete trials, makes these patients unavailable to test different therapeutic strategies, and substantially increases trial costs. If costs are higher, then fewer new ideas can be tested with available resources (thereby further slowing progress), and health care costs are driven up since drug sales must ultimately recoup the high costs of winning drug approval. Furthermore, if the population being targeted for accrual is small, then the requirement for large trials may preclude successful trial completion, and potentially effective agents may be abandoned due to inability to complete the RCT.¹ Even with relatively large targeted populations, a disturbingly high proportion of trials fail to meet accrual objectives.⁴ The overall challenge of achieving the criteria that would lead to regulatory approval of a new treatment is significant, such that as few as one in twenty initially promising novel agents eventually reach patients. The high price of new drugs is therefore not only a function of the expense required for specific development, but must also cover a company's costs (often substantial) for research on agents that never make it to market.

In order to prolong life, to reduce suffering, to improve cost-effectiveness and reduce health care costs, an objective must be to move rapidly and efficiently through the steps required for making effective new agents available to patients.^{1,2} These steps include discovery of new exploitable targets and of drugs focused specifically on these targets, rapid initiation and completion of trials in selected patient groups most likely to benefit from the therapy, optimization of biomarkers used to define these patient sub-populations, accelerated approval to give patients access to the new drugs they desperately need, and achievement of reduction in drug costs.

Cancer therapies as orphan drugs

“Orphan” drugs are agents that are of benefit in rare diseases.⁵ Development of orphan drugs is particularly problematic since there are often too few patients to permit the usual RCTs that may be required to demonstrate drug efficacy.⁶ Furthermore, if the disease is uncommon, then the market for the drug will be small once approved. This may make development of the drug unattractive to industry, since small markets may preclude recoupment of drug development costs.⁷ Since drug development costs must be recouped from smaller numbers of patients, the cost per patient treated may be very high, and this causes concern to those paying for health care.⁷ Approaches to this issue have varied across jurisdictions. Currently, in some countries, approval of drugs for selected orphan indications may be granted without requirement for RCTs if there is substantial evidence of drug activity,⁸ and the United States Congress recently passed the Food and Drug Administration Safety and Innovation Act to help expedite approval of “breakthrough” drugs that appear in early clinical trials to be highly effective.⁹ Alternatively, a variety of new RCT methodologies have been proposed to address the difficulty of conducting RCTs in rare diseases.^{6,10} Some governments also subsidize development costs for orphan drugs.⁷

In oncology, the perspective regarding what may be considered an orphan indication may soon change dramatically. Common cancers may be common since they may be caused by many different mutations, and patients with each type of mutation may require a different type of treatment.¹¹ Hence, some diseases that we regard as common are actually a collection of a large number of uncommon diseases that look similar, but that are each driven by a different potentially exploitable molecular alteration. For example, lung adenocarcinoma may arise due to mutations in *KRAS*, *EGFR*, *BRAF*, *PIK3CA*, *ERBB2*, *MAPK1*, or *NRAS*, by *EML4-ALK*, *ROS1* or *RET* fusion genes, by *MET* or *ERBB2* amplification or due to other alterations.¹²⁻¹⁴ To complicate things

further, only certain mutations in a gene may be associated with drug efficacy. For example, only some *EGFR* mutations are sensitive to erlotinib and gefitinib, while other *EGFR* mutations require different approaches.¹⁵

Furthermore, when patients with specific driver mutations are treated with a targeted therapy, they may become resistant due to a variety of different molecular events (each requiring a different therapeutic approach), and this may cause further splintering of subsets that are already small. For example, patients with lung adenocarcinoma and an *EGFR* mutation may initially respond well to erlotinib or gefitinib, but eventually become resistant due to emergence of an *EGFR T790M* mutation, *PIK3CA* mutation, *MET* amplification, epithelial-to-mesenchymal transition, conversion to a small cell lung cancer phenotype, or other reasons,¹⁶ and each acquired resistance mechanism may require a different therapeutic approach. Because of this multitude of potential causative mutations and mechanisms of acquired resistance, most malignancies, considered from this molecular perspective, can increasingly be viewed as orphan indications, with a large number of subpopulations, each with only a relatively small number of patients.

Since usual RCT designs require numerous patients, they may not be feasible in orphan indications, and alternative designs have been proposed.^{6,10} Tumor regression in response to a new agent may be a reliable endpoint.³ Tumors regress spontaneously only rarely, and hence, tumor regression in a high proportion of patients is a reliable indicator of drug effect. If serial measurements indicate a reduction in a tumor's diameter of >10%, there is generally less than a 10% probability that the apparent tumor regression was due to measurement error, and it is uncommon to have measurement error being responsible for an apparent tumor regression of >25-30%.^{3,17} Hence, when a new agent is used alone, major tumor regression in a high proportion of patients from a defined population is a reliable indicator of drug antitumor activity and should justify marketing approval for a drug,³ in keeping, in principle, with recent US "breakthrough" drug legislation.⁹ This approach could markedly cut

drug development costs and speed access to effective new therapies.

While suitability of response as the primary outcome variable in cancer clinical trials has been questioned, the major issues arise with drug combinations. When a new drug is added to standard therapy, one cannot rely on an increase in response rate (compared to historical controls) as an indicator of activity of the new agent, since the apparent improvement in outcome could arise entirely from variability in the background activity of the standard regimen to which the new drug is added.³ However, this is not an issue with single agents, and major tumor regression in response to a single agent is a reliable indicator of drug activity. Response to a single agent correlated very strongly with survival across a range of studies of chemotherapy and targeted agents,¹⁸ response rate in single agent phase II trials is a strong predictor of success in subsequent phase III trials,¹⁹ and FDA approval of anticancer agents based on response rate alone without a RCT has long been a successful and reliable strategy for orphan cancer indications.²⁰

Particularly important may be the ability of a new agent to generate responses in heavily pretreated patients refractory to standard therapies.¹ If a drug can only cause tumor regression in previously untreated patients, then it may be no better than other available agents, while if it can cause tumor regression in refractory patients who would not be expected to respond to older agents, this suggests important drug value.

While the most common type of orphan indication is likely to involve patients with a given tumor type that also share a specific molecular feature, there will also be instances where a specific feature may occur in patients with a variety of different malignancies, and a new agent may prove effective in the overall group of patients with the alteration, independently of tumor type. For example, BRAF inhibitors may work against both melanomas²¹ and lung cancers²² bearing *BRAF V600E* mutations (although BRAF inhibitors are less effective in *V600E*-mutant colorectal cancer due to activation of alternative signaling pathways²³).

Demonstrating drug efficacy

It takes far fewer patients to be confident of drug activity if one demonstrates a large treatment effect, and aiming high is an important component of speeding progress.^{1,3,10} Moreover, requiring a high degree of activity may encourage definition of biomarkers for optimal patient selection. Selecting patients based on the presence and expression of specific molecular modifications that are a target for an agent may result in very high response rates, while response rates are much lower in unselected patients or in patients selected based on biomarkers that are unlikely to be the direct drug target.³

With orphan indications, finding sufficient patients for even single arm studies can be challenging. Some studies have tried to overcome this by accepting patients from outside jurisdictions, but this often proves difficult since patients may not be able to afford to travel, and since payers may not cover costs associated with even the non-investigational components of the patient's management if the treatment itself is investigational and undertaken in a foreign jurisdiction.

Another approach is to open trials at multiple sites, but this requires each site to undertake the expensive and time-consuming process of study activation, and many such sites may end up not accruing patients despite their efforts. To overcome this problem, it is essential to explore creation of multi-jurisdictional virtual co-operative groups.² Trial approval in one accredited member institution would be sufficient for acceptance by research ethics boards in all member institutions internationally. This would require new, complex inter-governmental and inter-institutional collaborations, but the payoff would be huge. Major pharmaceutical companies currently conduct trials across multiple countries, but the costs associated with this are very high. Progress could be accelerated and costs of marketed drugs could be slashed if mechanisms were devised to expedite multinational collaborations. Patients, health care insurers and industry would all benefit.

To facilitate identification of patients with uncommon tumor types for specific trials, one recent approach has been to create individual

programs for large-scale screening for each molecular phenotype of interest. Alternatively, one may create enormous databases composed of banked bio-specimens and clinical data derived from patients who consent to be followed longitudinally and to be re-contacted for participation in trials should the molecular features of their tumors predict a benefit to them. In such an approach, pioneered by the Moffitt Cancer Center-led consortium, a readily available large scale population of clinical and biological data could be accessed in short order, and rare sub-populations of patients identified and directed to centers actively engaged in appropriate trials.²⁴

Increasing the rapidity of molecular screening of individual patients is also important. Several centers are exploring multiplex "reflex" screening by which pathologists immediately begin tumor molecular characterization at the time of diagnosis,²⁵ thereby making it possible to provide treating oncologists with tumor molecular characteristics when the patient is first seen. Currently, a major reason for patient inability to participate in trials is that they are deteriorating too rapidly to be able to await results of required screening tests. Very early initiation of these screening tests could largely solve this problem. While the cost of such molecular screening is high, it is miniscule compared to the overall high cost of clinical trials and compared to the enormous waste associated with treating patients with ineffective therapies.^{2,3}

Managing research costs

As noted previously, high clinical research costs slow progress since far fewer ideas can be tested with available resources,² they are a disincentive for development of orphan drugs that may only be appropriate for relatively small numbers of patients,⁷ and they translate directly into high drug/health care costs since research costs must ultimately be recouped from drug sales.² The high costs of clinical research are not driven just by the large numbers of patients required for RCTs but also by costs associated with complying with essential but poorly adapted regulations. Worldwide, regulators have a very difficult job in trying to ensure patient safety while simultaneously trying to expedite progress, and despite good

intentions, their efforts can be counterproductive. For every life-year potentially saved by enhanced regulations, many more life-years may be lost due to regulation-induced delays in access to effective new therapies, and the costs of complying with regulation may greatly exceed the value gained.² Hence, it is imperative that we assess mechanisms to streamline regulatory complexity without sacrificing safety and scientific integrity.

Patients and society could potentially garner enormous dividends from improving the cost-effectiveness of clinical research regulation, and there are numerous potential opportunities to make very large gains.^{1,2} For example, markedly excessive documentation requirements currently drive a disproportionately large component of clinical research costs, much of the data is never used,²⁶ and the massive piles of paper documenting factors that are of only marginal importance may bury and obscure clinical outcome details that are of high importance. We must rationalize documentation requirements.^{2,26}

Preclinical toxicology requirements could also be simplified,^{27,28} thereby cutting costs and permitting agents to enter clinical trials much faster. Preclinical toxicology generally only tells you the obvious (eg, that the drug will cause myelosuppression), or else predicts toxicity that ends up not being clinically important, or else misses toxicity that is later found to be clinically important. For anticancer agents, the only preclinical toxicology required is definition of the LD10 in rodents.^{27,28}

Furthermore, it can be predicted that using an approach that stratifies patients into their respective molecularly defined orphan diseases will result in significant restructuring of the current business plans of drug producers. While the specific patient subgroups of a given tumor type to be targeted for a given drug will be smaller, that same 'molecular subgroup' may be found in more than one tumor type, and may benefit from the new agent irrespective of tumor type. Moreover, the success rate for new drug development would predictably be much higher. A business case could be made for lowered drug costs in this new context.

Monitoring drug safety

Large studies are valued as a mechanism to assess drug safety prior to marketing. If drugs were approved without RCTs, then safety information would be available from relatively few patients at the time of drug approval. This will increase the importance of post-marketing surveillance, but it will be very important that surveillance processes be user-friendly, pragmatic and efficient rather than being expensive and cumbersome. To accomplish this, we would suggest exploration of new drug ordering and dispensing methodologies that would permit rapid and inexpensive collection of important safety and efficacy data post marketing of an orphan drug. One potential model that could work in Canada and that could be adapted for other jurisdictions would be as follows:

1. To initiate a new order, the clinician would complete and electronically sign the online form outlined in Table 2.
2. This would be submitted to a provincial funding authority that would pass all data through to regulatory agencies such as Health Canada while simultaneously issuing an approval number. The approval number would be required no matter who was paying for the therapy.
3. The approval number would trigger the submission to the most appropriate pharmacy of an electronically signed, approved prescription.
4. When filling the prescription, the pharmacist would submit electronically to Health Canada a list of all other medications that the patient is receiving (to permit monitoring for unexpected drug interactions).
5. When the prescription is to be renewed, the same processes will be followed, but the renewal form will include simple toxicity and efficacy information. (See Table 2.) Keeping the system simple, inexpensive and pragmatic would be an essential high priority.
6. Physicians would be encouraged to also submit the same type of form when the patient completes treatment or dies, to facilitate monitoring for late toxicity.

Using the same familiar form that is used for drug ordering will make it much easier for physicians to collaborate.

7. Health Canada staff assigned to the agent would monitor these toxicity reports, and would maintain an online database, supplemented by data from other jurisdictions and available to physicians.
8. The inclusion of efficacy information would provide helpful guidance for health care payers, and would clarify the extent to which the initial small clinical trials correctly predicted benefit in the target population.
9. Patients would also have options to provide online feedback on their personal experience with the agent.
10. Access to anonymized raw data would also be available to researchers worldwide.

The creation of this defined structure for pharmacovigilance would also provide the opportunity to examine the pharmacoeconomics of new drugs in the 'real world' context of our healthcare systems. It could provide an unparalleled opportunity to fully determine the magnitude of the predicted cost-benefits of personalized medicine.

The level of safety that is required for the drug would vary with the clinical indication. For example, in acute leukemia, it is accepted that therapy will generally cause severe, life-threatening toxicity, while much lower degrees of toxicity are considered acceptable for more indolent conditions. The most important thing is that clinicians be able to access up-to-date information on toxicity type and severity. Rather than a prescribed level of risk that is allowed, whether or not the therapy is used would depend on a frank, informed discussion between the physician and the patient.

Drug combinations

Drug combinations are now the standard of care as first line treatment for most metastatic malignancies, and use of new targeted agents in

combinations is likely to be key to prevention of emergence of acquired resistance. In order to speed progress, it is important to reduce barriers to exploration of innovative new drug combinations in orphan indications. Some of the steps outlined above for assessment of single agent therapies would also help with assessment of drug combinations, but there are some unique issues with combination studies. First, while we certainly share concerns about potential toxicity, it is imperative in the case of lethal diseases that this concern not slow down early clinical trials excessively.¹ Secondly, while there can be intellectual property issues in combining agents from different companies, the Cancer Therapy Evaluation Program at the US National Cancer Institute has taken steps to overcome these difficulties.²⁹ Overall, governments and academia must move decisively to create a framework to counter these challenges. Thirdly, as noted above, in a single arm study it is more difficult to determine whether a new agent added to a standard agent is adding benefit than it is to decide whether a new agent alone is active.³ Fourthly, some prior RCTs assessing drug combinations may have incorrectly concluded that the combination was ineffective since the impact of cross-over to study drug (or other effective therapy) was not taken into consideration, while other prior RCTs may have incorrectly concluded that a combination was effective since there was a comparison only to one component alone, without a planned comparison to sequential (non-combination) administration of the regimen components.³ Some potential study designs to address this have been described elsewhere.^{3,6,10} Using one of these study designs, the number of patients required for assessment can be kept to a lower number by using response or progression-free survival (rather than overall survival) as the primary endpoint, and by aiming for large improvements rather than just small improvements in outcome with the combination.³

CONCLUSIONS

We have made substantial progress in the treatment of cancer, but we have the ability to progress even much more rapidly in the future. To

reach our full potential will require new approaches to clinical research and to drug approval processes. New biological understanding of the complexity and diversity of cancer, combined with the increasing availability of highly targeted therapeutic agents are redefining

all aspects of our approach to novel cancer therapeutics. We suggest that there are increasingly strong grounds on which to question the feasibility, and even the ethics, of continuing to employ status quo clinical trials methods for the development and testing of new anticancer drugs.

TABLE 1 Abbreviations used

Oncogenes that may be mutated or amplified in human tumors:

BRAF: Murine sarcoma viral oncogene homolog B

BRAF V600E: mutation involving the V600 site of the activation loop of BRAF

EGFR: Epidermal growth factor receptor

EGFR T790M: mutation resulting in a threonine to methionine amino acid substitution at position 790 in EGFR

EML4-ALK: fusion between genes for Echinoderm microtubule associated protein like 4 and anaplastic lymphoma kinase receptor

ERBB2: Erythroblastic leukemia viral oncogene homolog 2 (Neuro/glioblastoma derived oncogene homolog)

KRAS: Kirsten rat sarcoma viral oncogene homolog

MAPK1: Mitogen-activated protein kinase 1

MET: met proto-oncogene (encoding the hepatocyte growth factor receptor)

NRAS: Neuroblastoma RAS viral oncogene homolog

PIK3CA: Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha

RET: ret proto-oncogene

ROS1: c-ros oncogene 1, receptor tyrosine kinase

Other abbreviations:

FDA: United States Food and Drug Administration

LD10: drug dose required to kill 10% of animals in preclinical toxicology studies

RCT: randomized clinical trial

TABLE 2 Potential design of online order and follow-up form

Order/report form for _____ (Agent) Date: _____

Patient name _____ DOB: _____ Health card #: _____

First submission Re-order Post-completion report of toxicity or death

Major Toxicity or Adverse Event, new since last report (Life-threatening, fatal, disabling or requiring hospitalization):

NA (first application for agent)

Unlikely due to agent: _____

Possibly due to agent: _____

Probably/definitely due to agent: _____

Minor Toxicity or Adverse Event (new since last report) that has not previously been known to occur with this agent:

NA (first application for agent)

Possibly due to agent: _____

Probably/definitely due to agent: _____

If patient has died:

Date of death: _____

Did toxicity from this agent contribute? Yes/probably No/unlikely Uncertain

Was there subjective/symptom improvement evidence of drug benefit at any time after it started?

NA (first application for agent, or patient did not have symptoms)

No/Unlikely

Uncertain

Yes/Probably

Was there objective (physical exam, scan, lab value, etc) evidence of drug benefit at any time after it started?

NA (first application for agent or scans, etc not yet repeated)

No/Unlikely

Uncertain

Yes/Probably

Additional comments:

Electronic Signature _____

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