What changes are needed to the current direction and interpretation of clinical cancer research to meet the needs of the 21st century?

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ABSTRACT

- In this 21st century, we will need to better analyse the outcomes of our spending on newer and more expensive anticancer drugs, particularly through postmarketing assessment, to ensure that these investments are justified.
- Evidence-based medicine is only as good as the evidence available, and we advocate for more independently designed and funded trials that concentrate on the minimum effective dose and duration of therapies to reduce toxicity to patients and to control costs. There is a place for governments to provide funding for these studies in the public good.
- Although improving survival over standard care is the gold standard for proving the efficacy of a new therapy, surrogate endpoints such as early biological marker changes, functional imaging changes or earlier measures such as progression-free survival must be investigated to enable drug therapies to be discontinued earlier if they are ineffective.
- Studies searching for the presence of biological targets must be funded to exploit the potential advantage of targeted therapies.
- Treatment guidelines are best written by experts who are independent of the pharmaceutical industry.
- Existing databases should be linked to better monitor the outcomes of new therapies. Privacy safeguards are important, but privacy legislation may need to be modified to serve the greater public good from the information gained from linking databases.

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Australia's ageing population has led to an increase in the nation's cancer incidence. The enormous costs of new treatments and medical interventions for cancer, and other diseases, continue to drive up health spending as a proportion of gross domestic product, rising from 8.5% in the 1997–98 financial year to 9.2% in the 2001–02 financial year.[1] If we are to continue to provide the best possible care for all cancer patients in Australia in the 21st century, we believe there needs to be a system to follow up and evaluate the outcomes of all treatments, particularly new and expensive treatments, more systematically than we currently do.

We are all impatient for cures for more cancers, and directing resources to clinical research is to be encouraged. However, our ongoing routine clinical use of increasing doses of varying combinations of current toxic and expensive cancer therapies, which will not result in cure or substantial remission in many cancers, consumes enormous amounts of finite financial resources that could perhaps be better spent in other areas.[2-6] Do we currently have enough information about the outcomes of new and often very expensive treatments, particularly after they are approved by the Therapeutic Goods Administration and listed on the Pharmaceutical Benefits Scheme (PBS)? These approvals are often based on data from very carefully selected subgroups of patients in studies that are often designed, funded and interpreted and written by the pharmaceutical company seeking the PBS listing. Conversely, do we know that important evidence-based clinical advances are reaching the communities for whom they were designed and approved?[7]

It is not being nihilistic to suggest that we need continuous assessment of the goals and outcomes of our research to justify continuing to fund high-cost cancer treatments. We maintain that the global management and funding of cancer therapy should be conducted by adhering to good governance principles. These principles include regular review, strict corporate governance of budgets and "profit and loss statements" (ie, comprehensive outcome assessments), careful strategic planning and the setting of realistic goals.

If we are to achieve the best possible balance in the future between improving overall outcomes for all cancer patients and maintaining affordable treatment, then we need changes. Improved outcomes data will help us to set realistic treatment goals for all patients. High-quality data can help patients and their health advisors to achieve the appropriate balance between efficacy and toxicity of the treatments for each individual patient. This high-quality data will also allow us to maximise the outcomes that we achieve from our investment into cancer treatment and research.

Evidence-based medicine is only as good as the evidence that is available. For example, a recent large randomised study using a new, expensive targeted therapy, panitumumab, in metastatic colorectal cancer, sponsored by panitumumab's manufacturer, reported an improvement in progression-free survival of only 0.7 weeks compared with best supportive care. The manuscript's conclusion presented it as an important and positive study.[8] The five authors who conceived and designed the study, analysed and interpreted the data, and wrote the manuscript included two employees and stockholders of the company and two physicians who declared significant potential conflicts of interest because they had accepted consultancy fees with or without honoraria from the same sponsoring pharmaceutical company. There was no difference in overall survival, although this assessment was impaired by the cross-over design.

Another large, randomised phase III study added the targeted agent erlotinib to gemcitabine in advanced pancreatic cancer. The manuscript concluded that this was the first study to demonstrate a statistically significant improved survival in advanced pancreatic cancer for any agent added to gemcitabine.[9] Seven of the study's authors declared a significant financial conflict of interest involving the manufacturer of erlotinib, the part sponsor of the study; two of the authors were employees of that company. However, the conclusion was based on an improved median survival of only

0.33 months (10 days), which would not be considered clinically significant, especially as it was achieved with considerable toxicity, including diarrhoea, infection, rash and stomatitis. A subsequent independent conservative analysis of costs showed that the incremental cost-effectiveness ratio of adding erlotinib to gemcitabine was US$410 000–US$510 000 per year of life saved.[10] Very few, if any, health systems can afford those costs.

A third recent, large, randomised non-crossover study added the expensive agent bevacizumab to paclitaxel for the treatment of advanced breast cancer. It showed no improvement in overall survival or in quality of life with the addition of bevacizumab, but was presented as a positive study because the combination improved progression-free survival.[11] This is a meaningless benefit if it doesn't help patients feel better or live longer, as progression-free survival has not been shown to be a surrogate endpoint for overall survival. Five of the authors declared potential financial conflicts of interest involving a company that makes or distributes bevacizumab.

In addition, we believe that the decline in independent studies in the past decade has seen a significant change in the design of clinical trials in cancer. There has been a shift away from using new drugs until maximum response and then stopping to avoid toxicity and re-treating at relapse, to studies that continue very expensive and toxic treatments until relapse, as long as they are tolerated, often requiring a 25% increase in measurable disease until the treatment is discontinued. There are no survival or quality-of-life data to support this increase in treatment duration, which adds enormous costs if this design becomes the "evidence base". An Italian study has been reported to show that phase III trials, multicentre trials, and international trials are less likely to be independent. As its author states: "It is ironic that our health systems risk bankruptcy for the skyrocketing costs of drugs that were developed on their own patients using strategies that ignore the patients' needs and priorities."[12]

The independence of guidelines

We need independent advice from some of the key advisory and policy-setting groups such as is provided by the independent Early Breast Cancer Trialists' Collaborative Group overviews from Oxford and the European Clinical Trials Directive,[13-15] and we need more independent Australian oversight of foreign clinical guidelines and industry-sponsored research.

Recent large and influential studies in breast cancer had designs and results that fitted "much better with the expectations of their sponsors than those of the patients and of the health systems that must sustain the costs of the new treatments".[12] We currently rely significantly on the interpretation of clinical studies and their incorporation into clinical guidelines by foreign clinical organisations, particularly those in the United States. However, many of these US guidelines are heavily influenced by the pharmaceutical industry and special-interest groups.[16] Questions inevitably arise when pharmaceutical companies and medical-device companies with a financial stake in the outcome provide substantial funding for their development and implementation, or when members of guideline committees also have substantial financial associations with industry.[17,18]

Databases to monitor outcomes

Australia has a system of cancer registries in each state and the Australian Institute of Health and Welfare pools data under strict guidelines to report national outcomes. It is difficult for independent research groups to obtain national data for outcomes analysis, as this currently requires individual ethics approval in each state. Ostensibly, this is because of concerns about privacy and the different data collection methods which makes aggregating the data more difficult. However, it is clear that this requirement for separate ethics approval in each state is also used as a mechanism to discourage use of national data by third parties who may make unfavourable comparisons of outcomes data between states.

Access to the best possible outcomes data will require a comprehensive national cancer database in Australia that provides data on outcomes for cancer treatments such as surgery and radiotherapy as well as drug treatments, something that is potentially more achievable here than in most countries. There are already voluntary national registries established, such as the Australian Rheumatology Association Database, which is monitoring the benefits and safety of new rheumatological drug treatments.[19] However, small individual databases for different diseases will provide only a small fraction of the information that a comprehensive national database would provide.

Potential solutions

Improving the evidence by trial design

We need more independently funded and reported research for our policy-setting groups to analyse.[20] To achieve this, the clinical research community needs to rethink the terms of its cooperation with industry in clinical trials, taking into account a wider clinical and public health perspective.[21] Resources may need to be directed to independent units. A large Danish study has shown that this approach, using stricter guidelines of good clinical practice as outlined in the 2004 European Clinical Trials Directive, led to an increase in registration of independent trials.[15] This strategy has the potential to be cost-effective in the long term and provide funds for governments to spend on pivotal clinical trials to be designed and run independently of the pharmaceutical company responsible for a product. This will improve the evidence on which treatment policy is based. Such studies would not maximise the use of a product, but discover the minimum effective dose and duration that would provide a cost-effective balance between efficacy and toxicity. An example is the use of trastuzumab in addition to chemotherapy as adjuvant therapy in breast cancer. The initial trials showed the benefit of 12 months of therapy with trastuzumab, which at the time cost A$50 000–A$60 000.[22,23] An independent Finnish study showed that 9 weeks of trastuzumab therapy in this setting was effective, but no comparison of relative efficacy could be made.[24] The next study designed by the pharmaceutical industry was to test 2 years versus 12 months of trastuzumab therapy, when a 6 months versus 12 months study was needed. Although this latter design was eventually initiated in France,[25] it stimulated debate about whether governments should fund such trials, given that the pharmaceutical industry is unlikely to do so, and there is potential benefit for the public purse.

Current infrastructure funding for cancer trials groups and a National Health and Medical Research Council (NHMRC) enabling grant through the Clinical Oncological Society of Australia is a suitable model for encouraging independent trials, but needs to be

expanded. The Australian New Zealand Clinical Trials Registry is also a useful resource for identifying the trials being performed,[26] and where the gaps exist.

Evaluation of trials

Traditionally, the strongest endpoint for a new agent in cancer therapy is a clinically meaningful survival advantage in a randomised clinical trial against the previous standard therapy, ideally with confirmation in a subsequent study. However, this endpoint can take years to achieve and is costly. The discovery of surrogate endpoints is vital to clinical investigation. These could be either (i) the observation of an early change in a biological endpoint, or an early change in findings on a functional scan, such as has been recorded with responsive gastrointestinal stromal tumours having early positron emission tomography responses;[27] or (ii) analysis of whether a progression-free survival endpoint does predict for a survival advantage in a particular tumour type. This type of research is vital to guide treatment decisions, and is beginning to be explored. However, clinicians will have to practise according to such evidence, particularly if regulatory bodies make a new drug available within a budget that is contingent on complying with early-stopping endpoints. This can be difficult if, in the absence of measurements showing early progression of the tumour, the emotive response of both the patient and clinician is to continue the use of a drug for longer.

The other essential for improving the cost-effectiveness of new targeted therapies in the 21st century is to identify the functional target before widespread use, and develop a funding mechanism to allow the target's detection, so that only patients whose tumours express that target receive the drug. This avoids the unnecessary toxicity and cost of treating patients who cannot respond. This lesson was learned in the early phase III trials of gefitinib in lung cancer, where the drug appeared ineffective in most patients because the actual genetic target had not been identified.[28]

Databases and linkage

One of the keys to more effective use of the national drug budget is better monitoring of outcomes after approval, and the ability to more easily modify the indications for use and reimbursement on the basis of emerging data from a drug's widespread use. In the US, the new Sentinel Initiative allows officials from the Food and Drug Administration to use information from Medicare claims to assess the risks of marketed drugs.[29]

In Australia, many of the data required for monitoring outcomes of drug therapies currently exist in the Medicare, PBS, Veterans' Affairs and individual state Cancer Council databases, and in state registries of births, deaths and marriages. The key is to be able to better utilise these data by linkage of databases. The potential benefits of this approach for the Australian health care system have recently been demonstrated with a large postmarketing study of trastuzumab therapy using these administrative databases.[30] A Western Australian program funded by the National Collaborative Research Infrastructure Strategy is piloting linkage of federal and state data. Other recent studies have also provided good insight into the potential benefits for our future health care of a comprehensive cancer database and the information technology capability for data linkage.[31,32]

Privacy legislation is often cited as a barrier to linking databases. The key question is whether the possibility of breaches of privacy, despite mechanisms that can be used in data linkage to protect individuals, is of such concern to the public as to outweigh the public good of using linked data for the purposes of postmarketing assessment of expensive and potentially toxic drugs. A simple survey asking patients in an Adelaide oncology clinic their views on use of their data for research did not indicate that privacy was an overwhelming concern.[33] Privacy legislation should be modified to allow linkage of population data, with the appropriate safeguards in place, if the potential public benefit is sufficiently strong.

Such a database may become partly self-funding if a "user pays" system for funding high-cost new therapies that was recently commenced in the United Kingdom is widely adopted.[20] These data will not only check that we are achieving outcomes that match the data that formed the basis of the PBS or Medicare funding approval of all treatments, but will also check the uptake of important clinical advances in the general community. Only then will we have this important part of our health service ready for the complex challenges of our ageing population and the rapidly increasing costs of new medicines in the 21st century.

Guidelines

Finally, we maintain that guidelines which translate research findings into practice and are influential on the practice of clinicians should ideally be written by experts with no potential conflicts of interest, and that transparency alone is insufficient.[34] These would be based on independent evidence as outlined above, and be updated with information from the improved outcomes surveillance made possible by linked databases. Further, the editor of *World Psychiatry*, Giovanni Fava, advocates that as well as enforcing declaration of potential conflicts of interest, we should reward those who choose to remain independent by giving them priority for public research funding, guideline panels and journal editorships.[35]

Competing interests

None identified.

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