ETHICS IN CANCER

NEGOTIATING LIMITS TO THE FUNDING OF HIGH COST CANCER MEDICINES

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Abstract

The cost of pharmaceuticals is overwhelming health budgets around the world. A growing proportion of this burden stems from the ever-increasing demand for subsidisation of cancer medicines. Those making decisions about which cancer medicines should be subsidised are often criticised by patients, clinicians and the pharmaceutical industry for withholding life-saving treatments from patients in desperate need. While their arguments are emotionally compelling, these critics often fail to recognise the complexity of resource allocation decisions, and the challenges faced by those making such decisions. In this article we describe two of these challenges: 1) the need for decision-makers to balance their desire to rescue those in desperate need against their responsibility to consider population-level opportunity costs and to make decisions based on solid evidence of cost-effectiveness; and 2) their need to negotiate ‘fair’ prices for medicines when they lack negotiating power, and when prices seem to be more reflective of what the ‘market will bear’ than what the medicines are really ‘worth’. We conclude that, while there is no easy solution to these challenges, there is a need for greater transparency and procedural fairness, so that stakeholders are both more alert to the complexity of decisions about funding high cost cancer medicines, and more willing to accept the outcomes of these decisions.

Cancer is one of the most active areas of contemporary drug development. According to the Pharmaceutical Research and Manufacturers of America, there are 98 drugs currently being developed for lung cancer, 87 for leukemia, 78 for lymphoma, 73 for breast cancer, 56 for skin cancer and 48 for ovarian cancer. In total, 3137 clinical trials for cancer drugs are being conducted in the US alone. Patients and clinicians often have high hopes that these new cancer therapies will be safe and effective, particularly because many of these medicines are ‘targeted’, or ‘personalised’ and therefore appear to be ‘designed’ with particular patients in mind. Success stories, such as imatinib for chronic myeloid leukemia, and trastuzumab for early, non-metastatic, breast cancer, bolster these hopes.

Driven by this optimism, patients and clinicians focus much of their attention on the need for regulators to approve cancer therapies as quickly as possible, and for public and private insurers (henceforth ‘payers’) to subsidise them. Governments have responded to this demand by establishing programs such as the UK’s Cancer Drugs Fund, and Australia’s Herceptin Program, which provide access to cancer medicines that have not been deemed to be cost-effective according to the usual standards applied by organisations such as the UK’s National Institute for Health and Care Excellence or Australia’s Pharmaceutical Benefits Advisory Committee. In Australia, growing expectations for access to expensive cancer therapies has also led to increased pressure on hospital therapeutics committees to provide access to expensive cancer medicines that are not listed on the Pharmaceutical Benefits Scheme or, alternatively, on the pharmaceutical industry to provide ‘compassionate access’ (also referred to as ‘patient access’, ‘compassionate use’, ‘named patient’ and ‘expanded access’), which makes cancer medicines available, either for free or at a discount, to patients who meet specific inclusion criteria. For example, for hematological malignancies, approximately 21% of patients receive non-Pharmaceutical Benefits Scheme funded drugs. Of these, 31% receive access through industry or hospitals, 61% through clinical trials, and 37% have to draw on savings, sell assets, take out loans, or fundraise to help pay for their treatments.

There has also been a recent growth in calls for ‘coverage with evidence development’, a type of ‘managed entry’ in which payers subsidise cancer therapies that have not been conclusively demonstrated to be safe and/or effective, with a view to subsequently generating evidence to support either ongoing subsidisation or disinvestment. Coverage with evidence development arrangements is already in place for selected cancer therapies in the US, UK, Europe and Australia.
Complexity and conflict in decisions about access to cancer medicine

There is of course, nothing wrong with patients and clinicians lobbying for access to cancer therapies, or with policymakers changing their processes to facilitate such access. But health systems globally are struggling to cope with this demand. A prediction that global spending on cancer medicines would reach $100 billion by 2018 saw this threshold passed in 2014, with almost 50% of this spending associated with new, targeted therapies.\(^1\)\(^2\)

The economic challenges associated with funding cancer medicines are evident in the recent streamlining of the UK Cancer Drugs Fund,\(^3\) and ongoing concerns about its viability.\(^4\) Similar concerns have been expressed about Australia’s capacity to cope with the growing demand for cancer medicines, with a recent Senate report acknowledging that expensive cancer medicines are a major challenge for governments attempting to balance affordable access while maintaining a sustainable health budget.\(^5\)

Given the strain placed on health systems by cancer medicines, it is crucial that those advocating for access to cancer medicines have a sophisticated understanding of the values that regulators and payers have to consider when they make their decisions. That they have a good understanding of why cancer medicines cost what they do, and why it can be so difficult for payers to negotiate fair prices is also important.

Competing values in decisions about access to cancer medicines

Those making these decisions about access to cancer medicines need to contend with a number of competing moral, clinical, economic and scientific values. Broadly speaking, these can be summarised as the desire to:

1. provide benefit to patients, without harming them, and to fulfill the related ‘rule of rescue’, which is the moral and psychological imperative to help those in desperate need, irrespective of cost or scientific uncertainty;\(^6\)
2. achieve equity - that is, ensuring that patients are not disadvantaged simply because they have rare cancers or, in the case of targeted cancer therapies, rare subsets of cancers;
3. allocate resources efficiently - that is, producing the ‘greatest good for the greatest number’ in an affordable and cost-effective manner, and paying a ‘fair’ price for medicines, based on their clinical value; and
4. make decisions based on sound scientific evidence of effectiveness, safety and cost-effectiveness.

Each of these values can be particularly difficult to fulfill in relation to cancer medicines. First, cancer medicines are not always as safe and effective as hoped. In many cases, decisions to provide access to cancer medicines are based on surrogate outcomes such as progression-free survival, so prediction of their true clinical benefit can be difficult. Cancer medicines also have serious and costly side-effects. For instance, up to 22% of cancer patients treated with chemotherapy are estimated to require hospitalisation for neutropenia.\(^7\) Even targeted cancer therapies, which are touted as being both safer and more effective than standard chemotherapies have their risks. For example, trastuzumab has been found to be associated with serious cardiotoxicity when combined with adjuvant chemotherapy.\(^8\)

Efficiency and affordability can be difficult to achieve because, as discussed above, cancer therapies are often so expensive, stretching health systems to their limits, and creating enormous opportunity costs. Achieving equity can also be challenging because, unless medicines are subsidised nationally, access to medicines is contingent on ad hoc decision-making by hospital therapeutics committees or by pharmaceutical companies.\(^9\) In the absence of these mechanisms, only the wealthiest patients, or those with the necessary connections for personal fundraising, can afford to pay for their own cancer therapies.

The desire to make decisions based on sound scientific evidence of effectiveness, safety and cost effectiveness, that is, to adhere to the principles of evidence-based medicine, can also be extremely challenging in relation to cancer medicines. One reason for this is that patients are often desperately ill and are often not willing to be subjected to the ‘control’ treatment in cancer clinical trials, or want to ‘crossover’ to the active treatment when their disease progresses.\(^10\)\(^11\) The increasing number of targeted cancer therapies in development exacerbates these difficulties because there is often a lack of evidence of their safety and efficacy from systematic reviews and meta-analyses of large, placebo-controlled randomised control trials (RCTs). This is primarily because RCTs and meta-analyses of targeted therapies can only be conducted when diseases and/or biomarkers are common, exemplified by the BCR-ABL translocation in chronic myeloid leukaemia, the HER-2 mutation in breast cancer or the EGFR mutations in lung cancer.\(^12\)\(^13\) In many cases, however, populations with specific biological profiles are very small, which means that, unless effect sizes are very large, the conduct of trials of targeted therapies comparable in power to the standards demanded by conventional RCTs can be challenging. There are also a number of other challenges associated with conducting RCTs of targeted cancer therapies, including the need to evaluate companion diagnostics alongside targeted therapies, and the difficulties associated with determining which patient group to select as the comparator in trials of targeted therapies.\(^14\)\(^15\) While there is currently a concerted effort to develop epidemiological and statistical methods for dealing with these challenges,\(^16\)\(^17\)\(^18\) regulators and payers are still challenged by calls to soften their commitment to the
principles of evidence-based medicine in order to allow access to targeted cancer therapies.\textsuperscript{29}

The abovementioned moral, clinical, economic and scientific principles are not only difficult to achieve in isolation, but can also be in tension with each other. These tensions are evident in the frequent news reports of patients who have been ‘refused’ access to the ‘only’ cancer therapy that could have ‘saved their life’.\textsuperscript{30,31} In these accounts, narratives of benefit, rescue and equity are typically countered by arguments about avoiding harm, ensuring affordability and cost-effectiveness, and adhering to the principles of evidence-based medicine. Similar competing principles are evident in the efforts of some pharmaceutical companies and disease advocacy groups to persuade regulators and payers to be more supportive of cancer medicines, and to facilitate access to them even if they are not, or have not been shown through RCTs to be, effective or ‘cost-effective’ according to the criteria usually used by regulators and payers.\textsuperscript{5,32}

**The challenges of negotiating fair prices for cancer medicines**

While those conducting health technology assessments of high cost cancer medicines have traditionally focused most of their attention on evidence of effectiveness and cost-effectiveness, payers are becoming increasingly concerned about the price of new cancer medicines. One example of a high cost cancer medicine recently approved is pembrolizumab (Keytruda), used to treat patients with melanoma, which is expected to cost approximately US$120,000 per patient per year.\textsuperscript{33,34}

While payers who question high drug prices are often criticised by the pharmaceutical industry for being naïve about the costs associated with drug development, they are in fact more concerned about whether the prices being asked for new medicines are ‘fair’. In this context, a fair price is one that reflects the amount that a company needs to charge in order to recoup the costs of drug development, continue to innovate, and make a reasonable profit for its shareholders.

Payers who want to negotiate such fair prices find themselves in a difficult position because there is currently no agreement as to how much development really costs a new medicine. Researchers from the Boston-based Tufts University Centre for the Study of Drug Development have recently estimated that it costs $2.6 billion to bring a new drug to market, with $1.4 billion attributed to direct costs of development and $1.2 billion attributed to investment returns necessary to attract investors. This estimate also accounts for drugs that have failed at some stage during development.\textsuperscript{35} This figure has, however, been contested by a number of people who claim that it does not account for public contributions to R&D, exaggerates the return on investment required to attract investment, and ignores experience showing that drugs can be developed for much less than the Tufts figure suggests.\textsuperscript{36,37}

In addition, although pharmaceutical companies often complain about the enormous risks and costs they bear, the industry remains highly profitable in comparison to other industries highly dependent on R&D, while up to three to 37 times more profitable according to some.\textsuperscript{38} Only 1.3% and 13% of revenue is channelled back into basic and clinical research respectively.\textsuperscript{39} There is, of course, nothing wrong with companies making profits, but the pharmaceutical industry receives extensive public support in the form of incentives and tax breaks. In return for this, there is the expectation that the industry will not exploit its success, but many people question whether the pharmaceutical industry is upholding its end of the bargain.

Sceptics thus believe that medicines are priced not according to what they cost to develop or what would constitute a fair return to shareholders, but rather according to what the ‘market will bear’.\textsuperscript{40} Given that the market for cancer medicines is dominated by a few regions, most notably the US and Europe, and characterised by lack of consumer autonomy, unlike other consumer goods, patients cannot simply choose whether to partake of cancer therapy, price insensitivity on the part of patients and clinicians,\textsuperscript{41} and information asymmetry regarding the cost of developing medicines, simply ‘letting the market work’ does not necessarily lead to fair prices for cancer medicines.

**Negotiating limits to the funding of high cost cancer medicines**

When values conflict and there is no obvious means of resolving them, and when policy decisions are complex, focusing on procedural justice becomes extremely important. This entails educating all stakeholders so they can participate in, and critique decision-making. It also entails having clear frameworks in place for specific decisions. A useful framework that can be applied is that of ‘accountability for reasonableness’ which emphasises 1) public access to decisions and transparency about reasons for decisions (publicity); 2) relevance of reasons to ‘fair minded’ participants (relevance); 3) mechanisms for challenging or disputing decisions (appeals); and 4) regulation of the process (enforcement).\textsuperscript{42}

For such a process to be possible for the funding of high cost cancer medicines, far greater transparency will be required. At present, decisions about access to cancer medicines are often not made transparently, largely because of the perceived need to maintain commercial confidentiality.\textsuperscript{43} While it is understandable that companies would not want to completely reveal their commercial interests, especially about prices, without greater openness,\textsuperscript{44} it may be impossible to achieve accountability for reasonableness and, rightly or wrongly, people will be left with the feeling that their values are not being respected.
Conclusion

New cancer medicines hold great promise, but the demand for these medicines places enormous strain on health systems. Those making decisions about funding cancer medicines face two key challenges: 1) balancing their desire to rescue those in desperate need with their responsibility to make decisions based on solid evidence of cost-effectiveness and to consider population-level opportunity costs; and 2) their need to negotiate fair prices for medicines when they lack negotiating power and when prices seem to be more reflective of what the market will bear than what the medicines are really worth. If their decisions are to be understood and have legitimacy, then they need to adhere to the principles of procedural justice and "accountability for reasonableness." As a starting point, companies and payers will need to be far more transparent about both the cost of drug development and the process of resource allocation.

References

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