SUBMISSION TO THE PBAC GUIDELINES REVIEW

September 2015

1. Introduction

In 2014 Rare Cancers Australia released a report entitled "Just a little more time". The report relied on the European RARECARE definition of rare cancers as being an incidence of less than 6 per 100,000 per year and supplemented this with a definition of "less common" cancers as being an incidence of between 6 and 12 (inclusive) per 100,000. In brief the report showed the following:

- Incidence and Mortality increasing at twice the rate of population growth due in large part to the ageing of the Australian population. **Mortality from rare and less common cancers accounts for half of all cancer deaths in Australia**
- Using Incidence to Mortality ratios as a proxy the report showed **no significant change in overall survival rates over the past 20 years for these cancers**
- A disproportionately small spend on medicines for these cancer patients **(less than 15%) through the PBS** when compared to both incidence and mortality
- A similarly small spend on research for these cancers – less than 20% with almost all these funds targeted at less common cancers and a token funding only of rare cancers

In short the challenges inherent in treating very small patient groups has conspired to realise a current environment whereby these patients are completely excluded from the progress achieved for those with more common cancer variations. **Action is needed now.**

Imagine the following scenario. Two Australians, both aged 55, both employed in the same role for 40 years paying the same amount of tax and both diagnosed with cancer on the same day – one cancer is common and the other is rare. Both patients consult the same oncologist who determines after consideration that they should both be treated with the same medicine. In the case of the patient with the common cancer his treatment is fully funded through the PBS. The rare cancer patient, in contrast, must find $7,000 per month to pay for his treatment simply because his disease is rare.

Australia prides itself on the "fair go" for all. There is nothing fair about the above situation and it is happening every day all over the country.

2. The Cancer Challenges

i. Multiple Indications

The rapid development of so many new types of cancer medicines has been accompanied by a much greater and deeper understanding of the myriad diseases that we refer to under the "catch all" banner that is cancer. Cancers or neoplasms are the uncontrolled growth of new cells within the body. These cells avoid control by the body's immune system and are constantly mutating or evolving in a way that assists their survival, even when under attack from cancer medicines or other treatments.

In recent times, scientists have come to understand that their formation and characteristics are not necessarily related to the site of the body in which they form but the genetic profile of both the patient and the cancer cells themselves.

This has led to treatments being developed that have widespread application across many cancers as we understand them today but their rapid approval is limited by a regulatory system that sees a medicine for melanoma as different from a medicine for lung cancer. In fact, the same medicine, acting in the same manner, could be highly efficacious for both conditions.

The current approval process, via the PBAC, doesn't recognise this development in science and its impact is most strongly felt in the lack of utilisation of existing cancer medicines for treatment of rare cancers.

ii. Multiple treatments

As discussed above, one of the great challenges with cancers is their capacity to constantly mutate meaning that whilst one treatment may be effective in destroying a large percentage of the diseased cells, a separate portion may have mutated in a way that is resistant to that one treatment. Consequently, the medical profession is increasingly using medicines in combination rather than sequentially.

These combination treatments facilitate the simultaneous destruction of the multiple mutations of the cancer cells in a way that sequential application of medicines cannot.

Hence the challenge for our current processes is to address the fact that cancers, as a group of diseases, attack our health in a unique way and cannot be effectively treated using the same processes that are in use for widespread uniform diseases such as diabetes or heart disease.

iii. One medicine – many cancers, many combinations

To allow our clinicians the flexibility they need to tackle cancer and to allow downstream processes such as the PBAC to operate quickly, there is a need to look at how treatments are related to indications and treatment combinations. For example, there has recently been significant development around new treatments for Melanoma known as PD-1 Inhibitors.

As the system currently stands, their introduction to Australia will be focussed solely on Melanoma. What we already know, however, is that there is strong evidence that these treatments will be efficacious in a range of other cancers, particularly rare types, where the key characteristics are similar.

Similarly, clinicians may wish to use new treatments in combination to enhance the prospects of success. It is therefore necessary that we consider how these developing treatment regimens are considered within the current regulatory framework.

3. The Problems

When evaluating a new medicine for funding there are a number of things that need to be considered. The more significant of these are listed below:

- The system relies very heavily on large scale evidence of improved overall survival. This creates problems where new drugs are proving so effective in trials that “cross overs” are deemed ethically necessary to provide optimum patient care. The current evaluation method struggles to accommodate this and “cross overs” are considered to weaken the evidence base for a new medicine.
- The quality of evidence appears to depend very much on the quantity of clinical trial participants. i.e. the larger the trial numbers, the more compelling the results. With rare cancers it is often difficult, if not impossible to achieve large trials. The link below is to a paper where the trial took 3 years to identify 50 patients with the target mutation.
  http://m.jco.ascopubs.org/content/early/2015/02/03/JCO.2014.59.8334.full
- Similarly, the cost to pharmaceutical companies of making submissions can mean that it is impractical and uneconomic for them to make a submission where the market is small, cost is high and the evidence is unlikely to have sufficient patient numbers to receive a positive recommendation or realistic price level. For example, a drug that is effective in both a common cancer and a rare cancer may never be approved for the rare cancer because the work required to prepare a submission is not commercially viable given the small patient population (market).
- “Off label” usage of existing medicines is not unusual among oncologists, however there is no mechanism in place whereby an oncologist can present a case to the authorities that there is a “plausible hypothesis” for the funded use of the drug in question. This is currently achieved either by requests for compassionate access to medicines from the pharmaceutical companies, by the patient paying to access the medicines or in extreme cases, the clinician is forced to “misdiagnose” the patient to gain access to the optimal treatment.

- On average, once a medicine is registered with the TGA, it may reportedly take a further 31 months for it to be approved for listing on the PBS. Time delays are a function of both administrative process and extended approval chains.

The issues raised above when combined with the rate of development of new cancer therapies means the current mechanisms are under extreme stress and this is causing a breakdown in the established processes. The combination of large numbers of therapies, high costs of development and small population groups are creating a perfect storm where both government and industry are struggling to make the current system work for RLC cancer patients.

4. The Challenge

The primary challenge is to allow clinicians to prescribe medicines that they assess will be effective for their patients without regard to the financial position of the patient. That is NOT currently the case.

The challenge therefore, is to find a mechanism whereby Australians suffering from RLC cancers can receive equitable and fair access to medicines that have reasonable, proven safety and efficacy for those diseases. To do so, the mechanism would need to cater for the following situations:

1. Drugs that are TGA registered for an indication but have not yet completed the PBS process or been assessed by the PBAC for that indication.
2. Drugs that are registered for one indication but are also considered to be applicable for other indications. As clinicians understand the more and more about the genetic drivers of cancer the science increasingly supports this situation. Technology is outstripping our regulatory process.
3. Drugs that are TGA registered and PBS listed for one or more indications but are also applicable to other indications for which, for whatever reason, no applications have yet been made.
4. Drugs that are registered in the US or Europe but not yet TGA or PBS approved here. The most common reasons for these types of situations is that their small population groups make it both commercially unprofitable and technically difficult to accumulate trial evidence and fund subsequent submissions.

5. The Role of Clinicians

It is expected that a patient seeing a clinician will have their treatment determined by that clinician based on his qualifications, knowledge and experience. Where drugs are funded through the PBS this is exactly what happens.

However, where a drug is not funded for the particular indication that afflicts the patient, the clinician is faced with less optimal choices, namely:

- Prescribe a “second choice” medication that is funded through the PBS.
- Seek compassionate or charitable access to the first choice medicine through a compassionate program or clinical trial. This option is not always available.
- Present the facts to the patient and let them decide if they can fund their own treatment.
- Deliberately misdiagnose the patient so that the patient can access the treatment through the PBS for a funded indication. **In these circumstances we are confronting clinicians with the choice of fraud or inadequate care.**

Australians believe their care should be determined by their clinicians – they entrust their lives to their doctor. Clinicians are among the most educated, respected and trusted professionals in our society and cancer physicians, in particular, deal with life and death situations every day. **It is essential that they have a louder, more authoritative voice in the determination of funded patient treatment.**

6. Case Studies

The current deficiencies in the system are so profound that our organisation has been moved to establish a charitable Cancer Medicines Fund under the campaign banner of Sick or Treat. The associated website is listed below. ***That we needed to establish this site says everything we need to say about the current state of cancer medicines in Australia***

In the first of our patient examples, Anita, has been diagnosed with non-small cell lung cancer and has been diagnosed as having an ALK+ genetic mutation as a contributing factor. Her oncologist prescribed a drug called Crizotinib and Anita has responded well for a number of months. Crizotinib has been recommended for listing by the PBAC for Anita's cancer but as the contractual process unfolds, it may yet take some months for it to be listed. In the meantime our Cancer Medicines Fund continues to fund her treatment at $7,400 per month.

Our second patient is Lillian who has also been diagnosed with non-small cell lung cancer but in Lillian's case her much rarer mutation is in the ROS1 gene. Her highly respected oncologist has also prescribed Crizotinib as there is substantial evidence of benefit. Lillian is also responding well but because her cancer or indication is so rare there is currently no application to PBS for re-imbursement.

Hence we face a situation where both Lillian and Anita need to self fund today at a cost of over $7,400 per month yet simply because of the random genetic mutations they have, Lillian will never receive funded medicines through the PBS whilst Anita hopefully will.

Same cancer, same treatment but no fairness. Both these patients benefit from the Cancer Medicines Fund and we refer the Review Panel to www.sickortreat.org.au for further information. *Note: Only information previously published is included about these patients.*

7. How could the PBAC Guidelines be adapted to help RLC cancer patients?

8.1 Addressing the 'problem with rare'

There is no doubt that our current system "has a problem with rare". The PBS has served Australia well with its principle of "the greatest good for the greatest number" but we need flexibility and change if we are to expand its reach to include the "greatest number of diseases", be they rare or common.

RCA therefore recommends that the PBAC take a proactive approach to ensuring that RLC cancer patients can access the medicines they need. Under the existing PBAC principles, as discussed earlier, *'when a medicine is used to treat a rare disease or disorder (defined as having a prevalence of ≤2000 individuals in Australia), it can be identified by the TGA as an 'orphan medicine'. **PBAC is aware of, and sympathetic to, the difficulties faced by sponsors of orphan medicines**'.*

Despite these sympathies towards orphan medicines, the majority of cancer drugs that are available for RLC cancers are not orphan, for example the PD-1 inhibitors, while being effective in a number of rare indications, are already listed for melanoma and other more common cancers.

We must therefore now take action to ensure that medicines, that are not technically orphan, because of their use in common cancers, are treated as orphans when under consideration for much rarer indications as recommended by the treating clinician.

8.2 Improve flexibility of the existing framework

8.2.1 Greater flexibility cost-effectiveness

RCA also recommends that the cost-effectiveness evaluation be broadened to allow costs other than direct medicine costs to be included. For example, an oral treatment with few side effects clearly costs less to society that hospitalisation for infusions – hence broader societal cost-effectiveness should be part of the process.

As highlighted earlier in this submission the PBAC principles for establishing cost-effectiveness are as follows: '***how the new listing compares with alternative medicines and/ or current standard care in terms of cost-effectiveness*** *('value for money'). To assess value for money, PBAC considers the clinical place, overall effectiveness, cost and cost-effectiveness of a proposed medicine **compared with other medicines already listed in the PBS for the same, or similar, indications**. Where there is **no listed alternative**, PBAC considers the clinical place, overall effectiveness, cost and cost-effectiveness of the proposed medicine compared with standard medical care.'*

This system of examining the cost-effectiveness has been used effectively over the years to sustain systems like the PBS and the UK's NICE scheme but its relevance to assessing new innovative treatments that are increasingly focused on small patient populations is limited.

Nowhere is this more readily seen than in the area of new treatments for rare and less common (RLC) cancers and the "off label" use of common cancer treatments for RLC patients. We must ensure that RLC cancer patients have access to the best available care, as directed by their treating clinician. This includes the PBAC considering whether the 'alternative' treatments available to these patients are suitable in today's treatment environment, and assessing whether it is ethical to provide RLC cancer patients with 30 year-old, cytotoxic chemotherapy treatments, when newer, more effective, treatments are available.

8.2.2 Greater flexibility with data requirements

In Australia today and in many other developed economies a regular process occurs of pharmaceutical companies (sponsors) preparing and lodging submissions to government regulatory bodies such as the PBAC for the re-imbursement of each and every single medicine, for every indication.

The current PBAC system is under severe strain and is characterised by:

- Lengthy delays in making life-saving or life–extending medicines available to patients in need;
- The imposition of significant cost being born by both pharmaceutical companies and government in assessing and analysing the cost-effectiveness of each drug;
- Restrictions on drug usage that disadvantage patients, hamstring clinicians and impose significant compliance costs on government. These restrictions can dictate when in the path of disease the medicine can be used and also in what types of disease they can be used; and
- **The intrusion of economics on the relationship between clinician and patient and as a consequence the clinicians inability to treat the patient in what the clinician believes to be the optimum manner.**

This problem is getting worse not better. Since the mapping of the human genome and the ability to better understand the molecular structure of many diseases, when combined with dramatic developments in technology and computer simulations, mean that in cancer today, over 900 new medicines are under development globally.

Many will be targeted treatments with small patient populations. The current model simply doesn't cope. Science is (as is common) developing at a much faster pace than the regulatory environment.

8. Conclusion

RCA welcomes this opportunity to provide this submission to the PBAC Guidelines Review. In this age of medical research, the greater understanding of the molecular biology of cancers and the advent of immunotherapies for treating cancer, it is critical that we ensure that the PBAC guidelines are capable of assessing the medicines of the future so that patients may have access at the earliest availability.

RCA recommends that there are a number of small changes that could be made to the current PBAC guidelines which would make them more flexible to assessing medicines for rare and less common cancer patients. The most obvious of which is to provide 'orphan drugs' status to medicines that are to be used for rare indications, even where the drug is already listed on the PBS for a more common cancer.

The second recommendations is to ensure that cost-effectiveness adequately considers other 'costs' associated with treating patients, and that the requirements are flexible enough to be able to establish whether the current 'standard of care' is sufficient and remains ethical.