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Comments on the 2013 Medicines Australia Oncology Industry Taskforce report: 'Access to cancer medicines in Australia'

Brain Tumour Alliance Australia Inc (BTAA) thanks Medicines Australia for initiating a discussion on the increasingly fraught process of developing, validating, and facilitating access to cancer therapies.

BACKGROUND ON BTAA

BTAA (www.btaa.org.au) is a national peer-led support and advocacy organisation for brain tumour patients, survivors, and their caregivers and families. It was incorporated as an Association in 2009 (ABN 97 733 801 179) and received Deductible gift recipient status in 2011. Brief information on BTAA can be found on the Australian Charities and Not-for-profits Commission website.

BTAA provides a Freecall service, authoritative patient/caregiver information materials, and in conjunction with funding partners hosts patient and caregiver support and information forums around Australia. In the interests of probity, it is notable that previous funding partners have included pharmaceutical companies and other health technology companies.

In the view of BTAA, such financial assistance has not influenced our impartiality in the past, and this remains true of the following comments.

Comments have been grouped under general themes discerned from the report.

THE SPECIAL CASE OF RARER CANCERS

BTAA agrees with statements in the report recommending that health technology assessment (HTA) authorities explicitly recognise any gains for 'poorer outcome' cancer types in the context of the very limited progress towards improved treatment options for these conditions.

As a general point, in the absence of definitive information on cost-benefit relationships, the PBAC should take a pragmatic view for poorer-outcome cancer types and incorporate some level of data collection and impartial analysis as a condition of interim inclusion in the PBS, together with a sunset clause whereby after a defined period, the clinicians and researchers experiences with using the medicine in patients can be impartially reviewed. Statements in support of such processes for less common or poorer outcome cancers have been made by BTAA at government inquiries in the past (*e.g.*,. see testimony to the Senate Finance and Public Administration References Committee's 2011 Inquiry into the Government's Administration of the Pharmaceutical Benefits Scheme; Committee Hansard, 25 July).

BTAA therefore agrees with the statements in the report that the US FDA multi-tiered system of 'fast-track', 'accelerated approval', and 'priority review' for cancer medicines should be considered and adapted for use in HTA and funding processes in Australia, particularly for the aforementioned condition types.

We wholeheartedly agree with the sentiment that: '…the collective burden of rarer cancers deserves attention, particularly regarding the increased incidence of some rare cancers among specific sub-populations.', and suggests that a highly relevant sub-population in the context of cancer consists of children, young, and middle aged adults.

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As consumers we ask that clinical trials endeavour to include means to measure overall survival, such as was demonstrated in the clinical trial of concomitant temozolomide and radiotherapy for the treatment of glioblastoma. However as human beings we do not accept a practice of withholding potentially beneficial salvage therapies to patients with rapidly progressing disease in order to maximise trial sensitivity for detecting overall survival (O/S) differences. From our reading of published literature (*e.g.,* see Saad & Buyse 2012. JCO. 30[15]), we believe that consensus expert opinion is that cross-over practices may indeed mask, to an extent, the O/S benefits imparted by superior therapies under evaluation. The use of historical control data (referred to as 'indirect comparator' in the report) matched as closely as possible to the study population, while imperfect, would likely assist determining effects on O/S in such circumstances. For this reason, BTAA understands that some researchers advocate that cross-over not be used in experimental therapies that still have not been demonstrated to be an effective salvage therapy (*e.g.,* see Saad & Buyse 2012. JCO. 30[15]). We agree that surrogate endpoints appear to be promising as substitutes to traditional measures such as O/S. Blood borne markers of tumour load appear to be of particular interest in that respect (*e.g.,* see Shao *et al,* 2012. Nat Med. 18[12]). In the here and now, however, there is a strong case that quality of life measures should be highly weighted when assessing treatments for cancer types with poorer outcomes.

As advocates of patients with a less common, poor prognosis cancer type, we ask that governments consider the special circumstances posed by these conditions, and reduce barriers to progress wherever these arise. In our view, a current barrier to access is lengthy waits to satisfy 'evidence tests' developed for far more common conditions. As consumers, we ask that industry consider prioritising such cancer types in R&D efforts for new medicines, while acknowledging that profitability must always be a consideration in publicly-traded companies. As citizens, we ask government to seek the lowest price when purchasing medicines on our behalf, provided this is not to such an extent that all commercial incentive is lost, and with it, access for patients.

FEASIBILITY OF CURRENT HTA PROCESSES

On the broader issue of 'evidence' and more general issue of continued advances in treatment, BTAA agrees with sentiments in the report that the 'traditional' means of drug development and subsidisation may not be best suited to the future problems facing developments in cancer care.

More innovative, cost-effective forms of 'evidence' should become acceptable to governments for the purpose of considering subsidisation. The most important evidence, and which should always remain mandatory to collect, is that novel treatments have acceptable safety profiles under the intended treatment regimen, relative to the current standard therapy(s). We therefore agree with previous statements of PBAC members that safety is always a primary consideration, but also ask that the high professionalism of clinicians be duly considered.

EVIDENCE, POPULATION-LEVEL STATISTICS & RCTs

In regards to statements such as an apparent: '…misalignment between [burden of disease] and healthcare expenditure', BTAA has long been concerned that the person-level view is being overshadowed by the otherwise commendable emphasis on 'evidence-based medicine', and by extension, evidence-based health policy including in HTA. This is particularly the case when comparing conditions that have far differing age profiles in terms of incidence and prevalence. Most would agree that a year of life lost at the age of (*e.g.*,) 16 is not equal to a year of life lost at (*e.g.*,) 80. However, aggregated population-level measures such DALY's and YLL's make such one–to–one comparisons.

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BTAA agrees with statements in the report that: '…total expenditure is a significant underestimate of the real cost of cancer'. BTAA would also note that in relative funding of cancer versus non-cancer conditions in the report, there is substantial cross-over due to comorbidities. For example, the well-established association between a cancer diagnosis and subsequent mental health disorders (*i.e,* anxiety, depression). For brain tumours, many patients have both a life-threatening condition (neoplasia), and a mental disorder(s) (anxiety/depression, cognitive sequelae, epilepsy, steroid induced personality changes, etc). Such disease-condition interactions do not seem to have been fleshed out in the report (e.g., Section 2.2.3); Nor do they seem to be an explicit consideration by the PBAC or other such Australian HTA bodies.

Another concern lay in the ephemeral nature of 'evidence' – what is evidence to one reasonable person may not be valid evidence to another. This is not necessarily due to conflicts of interest, but rather individual experience and particularly life experiences in the case of non-specialists (as discussed in the report). Although a good starting point, quantitative measures of 'need' should not be the sole determining factor in resource allocation decisions. If you have a prognosis of around 12 months – a not uncommon prognosis for cancer types with poorer outcomes – the chance to receive a few additional months from a beneficial, but not necessarily curative, therapy would likely be viewed as a much welcomed opportunity. We therefore agree that: '…seemingly small benefits may be of great significance to patients, and in a clinical context, especially for advanced cancer.', but suggest that early diagnosis is very rarely a relevant prognostic factor in cancer types of poorer outcomes.

BTAA agrees with the report's statement that rigid adherence to RCT's (randomised control trials) is not practicable for many cancer types, and may block access to useful treatments. We agree this is particularly true for co-dependent technologies. We have been contacted by a number of clinician-researchers regarding innovative therapies, such as 5-ala guided neurosurgery, intra-operative MRI, endoscopy, and PET-tracers in oncology, that they and published authors considered to be highly useful but who felt that subsidisation through *e.g.*, the PBS or MBS would be impossible due to the lack of RCT's, and through conflation between a 'drug' and a diagnostic tool. BTAA agrees with the statement that: '…many components of the current process are not fit for purpose to meet the emerging issues associated with cancer medicines.'.

The fact that adherence to rigid protocols can in fact impede advances in cancer treatment approaches is well described in the report. For example, there are over 120 different types of brain tumours, with quite uneven incidences between them, and obtaining sufficient patient cohorts for the conduct of multi-centre or large-scale single centre trials is very difficult. Public subsidy of new medicines could be redesigned to best facilitate patient-level (real world) research. There is great potential for a redesign in the subsidisation systems in Australia from the current situation of clearing 'proven' therapies using increasingly uneconomical, ineffective processes, towards instead being a partner in overcoming the information asymmetry faced by both private companies risking their capital, and patients weighing competing choices with only imperfect information.

TRANSPARENCY

In regards to comments about the transparency of decision making processes, BTAA restates its position put forward at the Senate Finance and Public Administration References Committee's 2011 Inquiry into the Government's Administration of the Pharmaceutical Benefits Scheme (Committee Hansard, 25 July 2011) that rather than only advising applicants, consumers should be given at least a brief description for the basis of any negative subsidy recommendation. Such

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information could be conveyed through a publicly available statement on a relevant Federal government website. BTAA therefore agrees with other stakeholders in the report who expressed concerns regarding the transparency in PBAC decisions.

FLEXIBILITY

BTAA agrees with statements expressing concern regarding differences between TGA/PBS approved indications and the emerging evidence-base, including Australian best-practice clinical care guidelines. In addition to the examples given in the report, there is the case of upfront temozolomide when used with concomitant radiotherapy in grade III anaplastic astrocytoma. This is in fact recommended in the Clinical Oncological Society of Australia's 2009 'Clinical practice guidelines for the management of adult gliomas', which states: 'Adjuvant chemotherapy *after* surgery and radiotherapy improves disease free survival and is recommended for patients with anaplastic astrocytoma'. Subsequent data from relevant trials (*e.g.*, CATNON; EORTC 26053-22054) have only strengthened the case for this protocol. What then, are people with anaplastic astrocytoma to make of COSA's recommendation, versus the PBS indication to only subsidise temozolomide at: '*Recurrence* of anaplastic astrocytoma following standard therapy'? BTAA therefore agrees with sentiments in the report that additional processes to include new indications for existing substances on the PBS are required in addition to reliance on 'user' (typically patent holders) initiated applications, particularly for off-patent medicines such as temozolomide.

INNOVATION

BTAA notes statements in the report pertaining to the loss of Australia's competitiveness as a destination for conducting clinical trials. We ask that all levels of government, non-government health providers, and industry continue to progress action items (Recommendations A to J) identified in the 2011 report of the Clinical Trials Action Group ('Clinically competitive: Boosting the business of clinical trials in Australia'). It is through such activities that costs for industry, governments, and the public can best be reduced, as the endeavour simultaneously marries cost-reduction with true innovation and patient access.

EQUITY

BTAA is concerned with the increasingly common situation where patients are resorting to fundraising activities to afford treatments that are either not subsidised, or to pay for overseas travel and insurance costs to access medicines that are not yet available in Australia. A recent example of the latter is the campaign 'Save Locky's Dad', in which Nick Auden is raising money to fund PD-1-antibodies (nivolumab and/or lambrolizumab) to treat his melanoma (see: www.savelockysdad.com). Access to potentially useful medicines should not be determined by a patient's/caregiver's ability to organise media campaigns. Continuation of such trends introduces a new form of inequality into the Australian healthcare system, one demarcated by popularity & influence (as discussed on page 56). Such issues of clout are already overly–influential at national-advocacy and decision-making levels. BTAA agrees with stakeholder sentiments relayed in the report that: '…the decision making process appears to have been driven by advocacy: popular cancers received stronger focus, whereas rarer cancers often received much less attention.'

Based on the opinions of clinicians published elsewhere, the TGA Special Access Scheme (also mentioned in the report) for unapproved therapeutics appears to be very difficult to utilise, and an inadequate means to bridge the gap between evidence requirements and timely access to promising new medicines.

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SUMMARY

The complexity of clinical trials only appears set to grow, with genetic, metabolic, proteomic, and other molecular data being more routinely incorporated into patient inclusion/exclusion criteria and utilised in stratification to interpret results. Increasingly, morphologically similar cancer types are being found to be separate conditions at the genetic/molecular level (*e.g.*, glioblastoma stratified by IDH allelism). The converse is also true, with morphologically distinct cancer types sharing identical genetic aetiology and therefore potentially being amenable to the same targeted therapy (*e.g.*, BRAF in certain melanoma and colorectal cancer types; see Sclafani *et al,* 2013. Crit Rev Oncol Hematol. 87[1]).

For these situations and for all rare diseases, strict application of the traditional Phase I to III paradigm and emphasising only overall survival is an approach increasingly likely to overlook and even impede true advances in patient care.

We agree with other stakeholders that for continued gains, the global regulatory system – Australia's included – needs to be reshaped to accommodate the increasing complexity of treatment modalities, the heterogeneity of patient populations and subsequent decreases in sample sizes, and the expectation of relatively smaller treatment improvements in the future that are still highly meaningful from the viewpoint of the affected individual. The clinical research methods of the past may indeed not be the best methods for the future, and this applies equally to subsidisation and other incentivisation processes.

BTAA believes that greater trust needs to be placed in the impartiality and professionalism of clinicians who ultimately decide whether to administer treatments, and in the decision–making abilities of patients/caregivers themselves.

We again thank Medicines Australia for initiating discussion on this highly topical subject.

Regards

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