Multiple Myeloma Stakeholder meeting outcome statement

23 May 2018, Department of Health, Woden ACT 2606

Attendees

Members of the Pharmaceutical Benefits Advisory Committee (PBAC), representatives of The Haematological Society of Australia and New Zealand (HSANZ), the Medical & Scientific Advisory Group (MSAG) of Myeloma Australia, The Leukaemia Foundation, Amgen Australia Pty Limited, Celgene Pty Limited, Janssen-Cilag Pty Ltd, Specialised Therapeutics Australia Pty Ltd and the Department of Health were in attendance.

Non-departmental attendees undertook confidentiality declarations and provided conflict of interest statements.

Purpose of meeting

The PBAC Chair outlined the goals of the stakeholder meeting as:

- to have an open discussion about the direction of clinical practice in multiple myeloma (MM) treatment within the context of high and uncertain cost-effectiveness for combination and ongoing therapies;
- to identify priorities for change in areas of highest clinical need; and
- to discuss the challenges for implementation and ways to address them.

The PBAC Chair acknowledged that changes to the current PBS listings for MM treatments will require advocacy from clinicians and patient groups, and co-operation from sponsors with the PBAC and the Department, and this stakeholder meeting provides an important forum to discuss ways forward.

Background

Misalignment of current clinical guidelines and PBS listings for MM treatments is an issue that been raised with the PBAC. At present, choice of therapy is driven by the PBS listings, which may not always match current clinical evidence for the ideal treatments to achieve optimal patient outcomes. In particular, the combined use of a protease inhibitor (PI), such as bortezomib, and an immunomodulatory agent (IMiD), such as lenalidomide or thalidomide, is standard in international guidelines for first-line treatment of newly diagnosed MM patients, however is not currently available through the PBS due to the restrictions in place. No submission for the combination of a PI and IMiD in this setting has previously been presented to the PBAC for consideration.

The PBAC works within a legislative framework where consideration of both clinical and cost-effectiveness is required, such that PBAC cannot recommend a therapy at a higher cost than alternative therapies unless for some patients, the new therapy provides a significant improvement in efficacy or reduced toxicity over the alternatives.

Recent PBAC considerations for treatments for multiple myeloma, including combination therapy with new agents (carfilzomib[1] + lenalidomide, and daratumumab[2] + lenalidomide or bortezomib) and maintenance treatment with lenalidomide[3] following an Autologous Stem Cell Transplant (ASCT), did not receive positive recommendations on the basis of high and uncertain cost-effectiveness.

Discussion and outcomes

Stakeholder responses

Prior to the meeting, the PBAC sought the advice of the MSAG, HSANZ, and the Leukaemia Foundation. The following section summarises the discussion of the issues raised at the meeting.

MSAG outlined the following issues of concern:

- The inconsistency of lenalidomide being available as a first line therapy for patients with newly diagnosed MM who are transplant ineligible (usually older patients) until disease progression, but unavailable as maintenance treatment for younger patients following ASCT who cannot access lenalidomide until after their MM has progressed.
- First-line treatment needs to be optimised. Combination PI and IMiD therapy in first line, preferably bortezomib + lenalidomide, is a high priority for improving overall survival for patients. Combination bortezomib + thalidomide would be a secondary option if the preferred option could not be achieved, or as an interim measure, but not as many patients would be able to tolerate this combination.
- Access to combination therapies with new agents, such as daratumumab or carfilizomib, in both relapsed disease and front-line is a priority; however achieving cost-effectiveness is complicated where there is more than one sponsor for the products in the combination. Should a restriction be approved for only one therapy for combination use (eg. only lenalidomide or bortezomib in combination with daratumumab), this would still be of clinical benefit, however MSAG stated that this was not optimal and would lead to an unsatisfactory outcome for patients particularly for those who appeared to respond better to the backbone treatment not available for use in combination.
- Access to thalidomide, which MSAG considered is an effective drug despite neurotoxicity, could be made easier if it could be utilised in conjunction with other PBS-sponsored drugs such as bortezomib, and if it was not categorised as a highly specialised drug.

HSANZ agreed with the points made by MSAG and highlighted that first-line combination therapies had the greatest opportunity to achieve a cost-effective outcome, given the most benefit in survival appears to be achieved through

[1] carfilzomib-psd-november-2016.pdf

[2] daratumumab-psd-november-2017.pdf

[3] pbac-outcomes/2018-03/first-time-decisions-not-to-recommend-03-2018.pdf

treatments in this setting; with diminishing incremental gains in later lines after multiple relapses. HSANZ was also of the view that wider use of thalidomide may also be a more cost-effective option and also raised the lack of flexibility in current prescribing, such as not being able to switch treatment dependent on response.

The Leukaemia Foundation noted treatment decisions are complicated and emphasised the confusion for patients in this space. With new therapies being very expensive and often taking some time between clinical trials and being made available on the PBS, it is difficult for patients to obtain the best treatment option.

Priorities and challenges

PI and IMiD combination therapy, first line

One of the highest priorities identified at the stakeholder meeting was increasing flexibility for prescribers in available treatments and combinations, especially in first line. There is a preference for access to PI and IMiD combination up front, with the possibility of triple therapy combination as new treatments, such as daratumumab, become available. The complexity in implementing changes to allow bortezomib (PI) in combination with either thalidomide of lenalidomide (both IMiDs) is establishing a cost-effective price for use in this context. Stakeholders acknowledged that while desirable, this challenge would be even greater for use of triple therapy in the newly diagnosed MM setting.

The PBAC Chair indicated that the committee would welcome applications for broader 'Multiple myeloma' listings for bortezomib and lenalidomide, which would provide greater flexibility for clinical decision-making. Sponsors indicated a willingness to work with the Department and PBAC to achieve broader listings. Sponsors highlighted the difficulties they face in the context of global considerations. However, it was also acknowledged that increase in volumes as a result of broader listings may provide some incentive for such an approach.

In discussion, it was suggested there are three types of patients with newly diagnosed MM, and patients would be roughly equally spread amongst these categories (approximately 1/3 of patients in each):

- Elderly, fit patients, not suitable for ASCT — triple combination bortezomib + lenalidomide + dexamethasone would be preferable, but only approximately one third of these patient would be suitable for this triple therapy. The remaining elderly, fit patients would be suitable for dual therapy (i.e. with either PI + dexamethasone or lenalidomide + dexamethasone). Another option would be triple therapy with PI + thalidomide + dexamethasone, but some patients may not be suitable for thalidomide (as bortezomib and thalidomide have similarly toxicity profiles).
- Elderly, unfit/frail, not suitable for ASCT — not generally suitable for triple combination therapy and would continue with dual therapy approaches (i.e. either bortezomib or an IMiD, both in combination with dexamethasone)
- Transplant eligible patients — many are adequately managed with current induction therapies. The use of a bortezomib + lenalidomide + dexamethasone may be preferable in certain sub-groups, eg high cytogenetic risk. Overall, there is less urgency for access to triple combination therapy in

this setting than for fit elderly patients. Although an estimated 40–50% of these patients access thalidomide in the post-transplant setting, access to lenalidomide in the maintenance setting is a priority.

Thalidomide combination use compared to lenalidomide combination use

Should the restrictions for bortezomib be simplified, there is the possibility of bortezomib + thalidomide combination use. Celgene, the sponsor of thalidomide, highlighted that there is no evidence comparing the safety and efficacy of bortezomib + thalidomide with combination use of bortezomib + lenalidomide, in either this setting or in triple combination with new therapies. The dominant clinical view was that it is possible/pragmatic to use thalidomide in settings where the effectiveness of lenalidomide has been demonstrated.

New agents and barriers to cost-effective combination therapy

Evidence for new agents, such as daratumumab, show combination use with lenalidomide or bortezomib can offer significant benefits to patients in the relapsed and refractory setting. Clinicians indicated a desire for use of daratumumab earlier in the treatment algorithm, not just for fit patients, but also less fit patients, ineligible for ASCT, who are likely to benefit from daratumumab in combination with a reduced dose of lenalidomide. While combination therapy with daratumumab was preferred to monotherapy, it was acknowledged that if used in combination with bortezomib, the bortezomib treatment will cease and daratumumab would be ongoing, as monotherapy, if patients had not progressed on the combination. It was further acknowledged that ongoing daratumumab monotherapy use as maintenance or consolidation therapy after combination treatment with bortezomib would offer a different clinical benefit to monotherapy daratumumab in a highly refractory population.

One of the key barriers to PBS listing for combination therapies with daratumumab, or carfilzomib, is that they are proposed for use in combination with another novel agent that is also high-cost. Thus, adding the cost of an additional new therapy without an equivalent additional gain in benefits makes it difficult to demonstrate cost-effectiveness, particularly when, such as in the case of lenalidomide, treatment is ongoing and therefore the extension in progression free survival also increases costs further.

Where different sponsors own the two novel agents in the combination, this creates further barriers to presenting a cost-effective submission. It was also acknowledged that once a cost-effective price is established and a positive PBAC recommendation was received, the Department could enter into negotiations with multiple sponsors in order to implement the recommendation. It was raised that Medicines Australia has a group reviewing this issue.

The PBAC reiterated that the PBS framework pays for health outcomes. The PBAC suggested it could consider a price and duration of therapy at which the new agents would be considered cost-effective, in the context of what would be considered a reasonable price for the current PI and IMiDs to be used in this extended setting.

Flexible prescribing and simplified relapsed and refractory restrictions

Clinicians raised concerns that the PBS restrictions do not allow switching of therapy from bortezomib to lenalidomide. For example, prior to progression, when it becomes evident through cytogenetic tests that patients will likely respond better to the alternative agent, prescribers currently cannot switch to the treatment until after the patient has progressed. In the relapsed and refractory setting it was raised that there were inconsistencies in prescribing requirements eg. barriers to use of pomalidomide other than in patients who had failed lenalidomide and bortezomib, whereas carfilzomib can be used after one prior therapy.

Clinicians indicated an interest in having greater flexibility to use pomalidomide, including in earlier treatment lines. Celgene highlighted that no clinical trials comparing pomalidomide directly with lenalidomide, or using pomalidomide in earlier lines of therapy, are available. The PBAC highlighted that the pomalidomide price, and therefore cost-effectiveness, is the main barrier to use earlier in the treatment algorithm and that similar issues of cost-effectiveness may influence differences in PBS restrictions across the MM setting.

Summary and next steps

The PBAC Chair thanked participants for their time in attending the Stakeholder meeting and considered the advice provided on the direction of clinical practice for MM and the priority areas for improving access to therapies to be valuable.

Clinicians highlighted the need for increased flexibility in prescribing, particularly in first-line treatments, where there is the greatest opportunity for achieving benefits. The key priorities identified for improving access were:

- bortezomib and IMiD combination therapy in first line
- lenalidomide available as maintenance therapy post ASCT
- simplification of restrictions in the relapsed and refractory setting.

The PBAC Chair noted that a simplified PBS listing of ‘Multiple myeloma’ for bortezomib and lenalidomide may address many aspects of these priorities. This may also more readily allow access to combination with new therapies, such as daratumumab, as they become available. However, price reductions would be needed in order for PBAC to be able to recommend the implementation of this change.

These simplified listings, by removing the current restrictions on therapy switching, would also allow clinicians greater flexibility in prescribing; particularly important should cytogenetic assessments identify the presence or absence of biomarkers which allow for targeting first-line therapy for best response.

The PBAC Chair indicated a willingness of the PBAC to consider simplification of restrictions in the relapsed and refractory setting, noting any requested changes would need to be considered in the context of the effective PBS prices.