Technology Guidance

Daratumumab-based regimens

for newly diagnosed multiple myeloma

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd), daratumumab in combination with lenalidomide and dexamethasone (DLd), and daratumumab in combination with bortezomib, melphalan and prednisone (DBMP) for inclusion on the MOH List of Subsidised Drugs for treating newly diagnosed multiple myeloma at the price proposed by the manufacturer.

The DBTd and DLd regimens have not been recommended in view of the uncertain extent of clinical benefit and uncertain cost-effectiveness compared with alternative treatments.

The DBMP regimen has not been recommended in view of low clinical need for this treatment in local practice.

Clinical indications, subsidy class and MediShield Life claim limits for daratumumab are provided in the Annex.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd), daratumumab in combination with lenalidomide and dexamethasone (DLd), and daratumumab in combination with bortezomib, melphalan and prednisone (DBMP) for treating newly diagnosed multiple myeloma. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for these treatments was considered in line with their registered indications. Additional expert opinion was obtained from the MOH Oncology Drug Subcommittee (ODS) who assisted ACE ascertain the clinical value of the treatments under evaluation and provided clinical advice on their appropriate and effective use based on the available clinical evidence.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1. The Committee noted that approximately 100 patients are diagnosed with multiple myeloma each year in Singapore. Upon diagnosis, patients are assessed for transplant eligibility based on several factors including age, performance status and comorbidities. Candidates for autologous stem cell transplantation (ASCT) are usually 70 years of age or younger and in good clinical condition.

2.2. About 40% of patients with newly diagnosed multiple myeloma are eligible for ASCT. Before undergoing transplantation, patients usually receive induction therapy to stabilise the disease. The Committee noted that bortezomib + lenalidomide + dexamethasone (BLd) was the standard regimen that was most commonly used as induction therapy in local practice, and daratumumab + bortezomib + thalidomide + dexamethasone (DBTd) was an alternative treatment option.

2.3. Among the remaining 60% of newly diagnosed patients who are not eligible for ASCT, those who are more fit are usually considered for treatment with BLd, or daratumumab + lenalidomide + dexamethasone (DLd). The Committee heard that BLd was a standard treatment in local practice and it was more commonly prescribed than DLd.

2.4. The Committee acknowledged that BLd was included in the MOH List of Subsidised Drugs, but they noted the clinical need to consider daratumumab-based regimens (DBTd and DLd) for subsidy to allow flexibility in treatment protocols and improve affordability for patients.

2.5. The Committee acknowledged that a four-drug combination of daratumumab + bortezomib + melphalan + prednisone (DBMP) had also been approved by HSA for treating patients with newly diagnosed multiple myeloma who are not eligible for ASCT. However, they heard from clinical experts that DBMP was not being used in local practice at the time of evaluation because melphalan-containing regimens were typically only used for palliative care, rather than in a frontline setting. Hence, there was low clinical need to consider DBMP for subsidy at this time.

Clinical effectiveness and safety

3.1. The Committee acknowledged that there were no head-to-head trials to show superiority of daratumumab-based regimens (DBTd and DLd) over BLd, which is the relevant comparator in local practice for treating newly diagnosed multiple myeloma.

3.2. For DBTd and DLd, the available clinical evidence showed that daratumumab, when added to bortezomib, thalidomide and dexamethasone (CASSIOPEIA trial) or to lenalidomide and dexamethasone (MAIA trial), provided an overall survival benefit in patients who were eligible and ineligible for ASCT respectively.

3.3. For DBMP, the Committee noted the clinical evidence from the ALCYONE trial in patients who were ineligible for ASCT, but acknowledged that the results were not relevant to the local setting since melphalan-containing regimens were not used as frontline treatment.

Cost effectiveness

4.1. The manufacturer of daratumumab was invited to submit a value-based pricing (VBP) proposal for their product for subsidy consideration. Based on the manufacturer's pricing proposal, the Committee acknowledged that the monthly treatment costs of DBTd and DLd were substantially higher than BLd for treating newly diagnosed multiple myeloma. The Committee also noted that the cost of BLd was expected to reduce further over time as more generics enter the market. Given the lack of evidence to ascertain the comparative clinical benefit of daratumumab-based

regimens versus BLd, the Committee considered that DBTd and DLd were unlikely to represent a cost-effective use of healthcare resources.

Estimated annual technology cost

5.1. Based on local epidemiological rates and estimated drug utilisation in the public healthcare institutions, the annual cost impact in the first year of listing daratumumab on the MAF when used as part of DBTd and DLd combination regimens was estimated to be:

- DBTd: less than SG$1 million for treating patients with newly diagnosed multiple myeloma who are eligible for ASCT; and
- DLd: between SG$1 million to less than SG$3 million for treating patients with newly diagnosed multiple myeloma who are not eligible for ASCT.

Recommendations

6.1. Based on available evidence, the Committee did not recommend daratumumab in combination with bortezomib, thalidomide and dexamethasone (DBTd), and daratumumab in combination with lenalidomide and dexamethasone (DLd) for inclusion on the MOH List of Subsidised Drugs for treating newly diagnosed multiple myeloma at the price proposed by the manufacturer, in view of the uncertain extent of clinical benefit and uncertain cost-effectiveness compared with alternative treatments.

6.2. The Committee did not recommend daratumumab in combination with bortezomib, melphalan and prednisone (DBMP) for inclusion on the MOH List of Subsidised Drugs for treating newly diagnosed multiple myeloma as there was low clinical need for this treatment in local practice at the time of evaluation.

ANNEX

Recommendations by the MOH Drug Advisory Committee

Drug preparation	Clinical indications	Subsidy class (implementation date)	MediShield Life claim limit per month (implementation date)
Daratumumab 100 mg/5 mL and 400 mg/20 mL concentrate for solution for infusion and 1800 mg/15 mL solution for subcutaneous injection	Daratumumab in combination with bortezomib, thalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are eligible for an autologous stem cell transplant.	Not recommended for subsidy	$2000 (1 Sep 2022)
	Daratumumab in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma who are ineligible for an autologous stem cell transplant.	Not recommended for subsidy	$2000 (1 Sep 2022)
	Daratumumab in combination with bortezomib, melphalan and prednisone for patients with newly diagnosed multiple myeloma who are ineligible for an autologous stem cell transplant.	Not recommended for subsidy	Not recommended for MediShield Life claims

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 27 May 2021, 2 July 2021 and 26 November 2021. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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