



ATC codes: L01AA01

Indication	Plasma cell myeloma ICD11 code: 2A83.1
INN	Cyclophosphamide
Medicine type	Chemical agent
List type	Complementary
Formulations	Parenteral > General injections > IV: 500 mg in vial powder for injection Oral > Solid: 25 mg tablet ; 50 mg tablet
EML status history	First added in 2019 (TRS 1021)
Sex	All
Age	Adolescents and adults
Therapeutic equivalence	The recommendation is for this specific medicine
Patent information	Patents have expired in most jurisdictions Read more about patents .
Wikipedia	Cyclophosphamide
DrugBank	Cyclophosphamide

Expert Committee recommendation

The Committee acknowledged the treatment of MM to be complex and recognized the need to provide the best available care within the context of both non-transplant and transplant settings. The Committee recommended the addition of bortezomib, lenalidomide and thalidomide to the complementary list of the EML for the treatment of multiple myeloma patients in both non-transplant and transplant eligible/ available settings, on the basis of good evidence showing large improvement in survival outcomes with acceptable safety for patients with newly diagnosed multiple myeloma. With regard to MM treatment in transplant-eligible populations, the Committee noted the additional evidence presented as part of the review process supporting standard regimens used in the induction phase before ASCT involving three-drug combinations: VTD (bortezomib, thalidomide, dexamethasone), VCD (bortezomib, cyclophosphamide, dexamethasone), PAD (bortezomib, doxorubicin, dexamethasone) and RVD (lenalidomide, bortezomib, dexamethasone); and of the benefit of lenalidomide maintenance therapy following ASCT. In the non-transplant setting, the Committee acknowledged that the proposed medicines are administered as part of treatment regimens involving companion cytotoxic agents and/or steroids (melphalan, cyclophosphamide, prednisone, dexamethasone). Accordingly, the Committee recommended the addition of melphalan to the complementary list of the EML for treatment of multiple myeloma, and that the current listings for cyclophosphamide, doxorubicin, prednisone and dexamethasone be extended to include multiple myeloma as an indication.

Background

The application requested the addition of bortezomib, lenalidomide and thalidomide to the EML for the treatment of newly diagnosed multiple myeloma patients in non-transplant settings. Treatments for multiple myeloma had not previously been considered by the Expert Committee for addition to the EML. [Abbreviations: M = melphalan, P = prednisone, C = cyclophosphamide, D = dexamethasone, V = bortezomib, R = lenalidomide, T = thalidomide].

Public health relevance

Multiple myeloma (MM) is the second most common haematological malignancy and accounts for 2.1% of all cancer deaths in the United States (1, 2). In 2018, 159 985 new MM cases and 106 105 MM deaths were estimated worldwide (3). Globally, myeloma caused 2.1 million disability-adjusted life-years (DALYs) in 2016 (4). Globally, the incidence rate increased by 126% between 1990 and 2016 and is strongly related to age (4, 5). The largest increase has been observed in low- and middle-income countries (LMICs) (4). Based on the latest statistics in the United States, the median age of myeloma diagnosis across all races and both genders is 69 years (2). In high-income countries (HIC), autologous stem cell transplantation (ASCT) is routinely used for younger patients with a good general state of health. However, ASCT is not available in many LMICs (3). Lack of access to general and specialized health care leads to wide disparities in survival rates between HICs and LMICs. In the United Kingdom, for example, 47% of diagnosed MM patients are predicted to survive at least five years (32.5% at least 10 years) (5). In comparison, a five-year survival rate of only 7.6% was recently reported in Nigeria, as a result of constraints in access to ASCT, unavailability of medicines for MM and delayed diagnosis with more advanced presentations and related organ failures (6). Of patients diagnosed with MM in Nigeria, up to one-third qualify for renal dialysis as a result of MM-related end-stage nephropathy (7). In non-transplant settings (no transplant-accessibility or transplantineligibility), the introduction of immunomodulatory drugs and proteasome inhibitors has led to an improvement in the overall survival of patients. A retrospective analysis of 631 patients, who received an initial therapy of bortezomib, lenalidomide or thalidomide, reported a median OS of 7.3 years (95%CI 5.9 to not reached). In comparison, a median OS of 3.8 years (95%CI 3.1 to 4.6) was reported for 425 patients, whose initial therapy did not include these agents (8). The lack of availability ASCT services is more common in LMICs. Some regions of the world lack access to stem cell transplantation entirely; for example, in sub-Saharan Africa there is no facility to deliver ASCT care for MM patients outside of South Africa (4). This raises the issue of a public health urgency requiring diversified actions including ensuring access to effective medicines, and building capacity for transplant services. The application focused on the transplant-ineligible/inaccessible setting, more applicable in LMICs, proposing the inclusion in the EML of bortezomib, lenalidomide and thalidomide to address an unmet medical need.

Benefits

The application presented the findings of a rapid Cochrane network meta-analysis conducted to compare the efficacy and safety of bortezomib, lenalidomide and thalidomide versus the former standard treatment of melphalan and prednisone (still used in many LMICs) for transplant-ineligible MM patients. Twenty-six randomized controlled trials (11 403 participants) were eligible for inclusion in the NMA: (Myeloma XI (9), EMN01 (10), FIRST (11), ECOG E1A06 (12), MM-015 (13), HOVON 87 (14), Myeloma IX (15), GBRAM0002 (16), Kim 2007 (17), Ludwig 2009 (18), TMSG (19), HOVON 49 (20), IFM 99-06 (21), GISMM2001-A (22), MM03 (23), IFM 01/01 (24), NMSG #12 (25), Katsuoaka 2013 (26), UPFRONT (27), VISTA (28), GEM2005 (29), Mookerje 2017 (30), SWOG S0777 (31), E1A05 (32), GIMEMA-MM-03-05 (33), NCT01274403 (34)). Included participants were randomized to 21 different treatment regimens involving fixed or continuous therapy with combination regimens involving melphalan (M), prednisone (P), cyclophosphamide (C), dexamethasone (D), bortezomib (V), lenalidomide (R) and thalidomide (T). Overall survival was measured for all 21 treatment regimens and a total of 11 071 patients. The network was not fully connected and consisted of three subnetworks comprising 30 pairwise comparisons. Compared to MP, four regimens showed a significant, clinically meaningful improvement in overall survival: Continuous VRDc (bortezomib, lenalidomide, dexamethasone) (HR 0.49, 95%CI 0.26 to 0.92), continuous VTMPc (bortezomib, thalidomide, melphalan, prednisone) (HR 0.49, 95%CI 0.26 to 0.93), fixed RD (HR 0.63, 95%CI 0.40 to 0.99), and fixed TMP (thalidomide, melphalan, prednisone) (HR 0.75, 95%CI 0.58 to 0.97). The estimated differences in median OS compared to MP were 37.4 months for VRDc and VTMPc, 21.1 months for RD and 12.0 months for TMP. The confidence in estimates for overall survival could be rated for RD, TMP, VMP, and VRDc. The use of RD, TMP, and VRDc for first-line treatment of multiple myeloma patients likely results in a large increase in overall survival (moderate confidence in estimates). The use of VMP as initial myeloma therapy may result in a large increase in overall survival (low confidence in estimates). The clinical benefit of the treatments was assessed in the application according to the ESMO-MCBS v1.1 (35). The application graded the magnitude of clinical benefit as 4 (survival benefit compared to comparator >nine months (36)) for VRDc, VTMPc, RD, RDc, VMP, RCPc and TMP. The Committee noted that to date, the ESMO-MCBS v1.1 has been validated only for solid tumours and that a version validated for haematological malignancies is in development. (Unpublished data of ESMO-MCBS ratings for the proposed medicines were shared with the Expert Committee). Progression-free survival (PFS) was measured for all 21 treatment regimens and a total of 10 389 patients. The network was not fully connected and consisted of four sub-networks comprising 29 pairwise comparisons. In general, continuous treatment regimens were superior to fixed MP, and 7 out of 11 compared bortezomib,

lenalidomide or thalidomide combinations showed a significant improvement of PFS compared to MP. The confidence in estimates for PFS could be rated for RD, TMP, and VRDc, but could not be rated for VMP, because VMP was not connected to MP in the network. The use of RD, TMP, and VRDc for first-line treatment of MM patients likely results in a large increase in PFS (moderate confidence in estimates).

Harms

Adverse events of Grade 3 and 4 were reported in nine studies for 13 treatment regimens in 3318 patients, however the studies were not comparable in NMA. Serious adverse events (SAEs) were reported in eight studies for 14 treatment regimens in 7306 patients. The relative risk (RR) for at least one SAE was similar across treatment regimens. The confidence in estimates could only be rated for VMP. There was moderate confidence in the estimates that VMP likely increases occurrence of SAEs (RR 1.28, 95%CI 1.06 to 1.54). Infections were reported in 15 studies for 17 treatment regimens in 7470 patients. The RR for infections tended to be slightly higher for patients receiving lenalidomide-based therapies compared to patients receiving thalidomidebased therapies. The RR for infections was also significantly higher in patients receiving continuous therapies compared to fixed MP. Polyneuropathies were reported in 18 studies for 19 treatment regimens in 8978 patients. The RR for polyneuropathies was the highest in patients receiving bortezomib-based therapies compared to MP (RR 88.22, (95%CI 5.36 to 1451.11) to 441.08 (95%CI 7.74 to 25 145.52)). The RR for polyneuropathy appeared to be smaller for patients receiving lenalidomide-based therapies, compared to patients receiving thalidomide-based therapies. Thromboembolism was analysed from 13 studies for 13 treatment regimens in 4 277 patients. The RR for thromboembolism was higher for patients receiving continuous therapy compared to fixed duration MP (RR 3.91, (95%CI 0.41 to 37.12) to 13.09 (95%CI 1.03 to 167.25)). Patients receiving a thalidomidebased therapy had a greater risk for thromboembolism compared to patients receiving bortezomib- or lenalidomide-based therapies, or MP. Withdrawals due to adverse events were reported in 16 studies for 19 treatment regimens in 7 052 patients. The RR to discontinue assigned therapy was greater for patients receiving double or triple drug combinations compared to MP alone (RR 1.06, (95%CI 0.63 to 1.81) to 8.92 (95%CI 3.82 to 20.84)). Study withdrawal was similar across bortezomib-, lenalidomide-, and thalidomide-based regimens. There was no difference between double versus triple drug combinations, or between fixed duration versus continuous therapy. The confidence in estimates for withdrawals due to AEs was rated for RD, TMP, VMP, and VRDc. Compared to MP, use of RD, TMP, and VRDc results in a large increase in withdrawals due to AEs (high confidence in estimates). Use of VMP probably results in little or no difference in withdrawals due to AEs (moderate confidence in estimates).

Additional evidence

The Committee also considered additional evidence, not presented in the application, for the treatment of MM in the ASCT-eligible/accessible settings. The standard treatment for ASCT-eligible MM patients involves induction therapy followed by high-dose melphalan and ASCT with lenalidomide maintenance. A meta-analysis of four studies (1572 patients) compared bortezomibbased induction therapy prior to ASCT with non-bortezomib-based induction therapy. The studies compared bortezomib-dexamethasone with vincristinedoxorubicin-dexamethasone (IFM 2005-01 trial); bortezomib-doxorubicindexamethasone with vincristine-doxorubicin-dexamethasone (HOVON-65); and bortezomib-thalidomide-dexamethasone with thalidomide-dexamethasone (PETHEMA GEM05MENOS65 and GIMEMA MM-BO2005). The bortezomibbased therapies were associated with longer PFS (+7.3 months; HR 0.75), longer OS (+5% at 3 years, HR 0.80) and greater activity (complete response rates: +14%, OR 2.05), compared to non-bortezomib-based therapies. Peripheral neuropathy was reported more frequently in bortezomib treated patients compared to non-bortezomib treated patients: 19% vs 7% (all Grade), and 3.3% vs 2% (\geq Grade 3) (37). A randomized controlled trial involving 525 patients with newlydiagnosed MM evaluated the efficacy and safety of the addition of bortezomib to lenalidomide and dexamethasone (SWOG S0777). Findings were consistent with the thalidomide-containing regimens: the addition of bortezomib to lenalidomide-dexamethasone was associated with gains in both PFS (+13 months, HR 0.71) and OS (+11 months, HR 0.71). Adverse events of Grade 3 or higher, and treatment discontinuations were also more common in the bortezomib-treated group (38). The Committee also considered the role of lenalidomide after ASCT, as maintenance up to relapse and maximal tolerance. A meta-analysis of three RCTs (CALGB/Alliance 100104 study, IFM 2005-02 Trial and the Italian GIMEMA RV-MM-PI-209) involving 1208 patients evaluated the effect of lenalidomide maintenance after ASCT in newly diagnosed MM. Lenalidomide maintenance demonstrated a significant gain in both PFS and OS: PFS in patients receiving lenalidomide was 29.3 months longer (HR 0.48, 95%CI 0.41 to 0.55). The 7-year survival rate was 62% with lenalidomide maintenance and 50% with placebo or observation (HR 0.75, 95%CI 0.63 to 0.90). The use of

lenalidomide resulted in more major adverse events than placebo. In particular, an increased risk of secondary malignancies was observed, 6.1% vs 2.8% with placebo/ no maintenance (39). The long-term follow-up data of CALGB (Alliance) 100104 study showed a meaningful and significant OS gain in patients receiving lenalidomide maintenance. After three interim analyses, the study was unblinded at a median follow-up of 18 months, at which point 86 (67%) of 128 patients without progressive disease in the placebo group chose to cross over to the lenalidomide group. The analysis of survival on the intention-to-treat population demonstrated an increase in 3-year OS of 8%, with 88% (95%CI 84 to 93) among patients in the lenalidomide group and 80% (95%CI 74 to 86) among patients in the placebo group (HR 0.62, 95%CI 0.40 to 0.95) (40). The Myeloma XI study more recently provided results consistent with the previous clinical trials of lenalidomide maintenance, confirming a gain in median PFS (39 months vs 20 months; HR 0.46, 95%CI 0.41 to 0.53; $p < 0.0001$) but not in OS (78.6% vs 75.8%; $p = 0.15$). The analysis was published at 31 months of median follow up (41). Notably, mature data for OS in ASCT-eligible settings require long-term follow up. For this reason, PFS and myeloma response rates have been agreed as valuable surrogate endpoints for OS and PFS is used as primary endpoint to assess the benefit of anti-myeloma medicines (42).

Cost / cost effectiveness

The application summarized the findings of a scoping review undertaken for economic evidence that addressed treatment regimens based on bortezomib, thalidomide or lenalidomide as first-line therapy in MM. The scoping review identified two cost-analyses (43, 44), one cost-impact analysis (45) and one retrospective study of claims data (46). Also identified was a health technology assessment report by the National Institute for Health and Care Excellence (NICE) (47). Reported incremental cost-effective ratios in the NICE technology appraisal ranged from £ 2234 per quality adjusted life year (QALY) to over £ 300 000, compared to MP depending on the intervention (47). A United States cost-analysis found the monthly on-treatment costs (drug cost, medical costs and AE management costs) were lowest for MP alone and highest for MPT. The total cost over 20 years for treatment with VMP and MPT were almost or over twice as high than with MP alone. Compared to VMP, MP was more effective with regard to costs per life-year and cost per QALY, while compared to MPT, VMP was cost-saving (44). A cost-impact model addressed the total costs associated with first-line treatment of newly diagnosed MM who were ineligible for stem cell transplant in France, Germany, Italy, Spain and the United Kingdom, modelled over five years. Three scenarios were evaluated and compared. A baseline-scenario represented the 2017 uptake of lenalidomide in the assessed countries. The market shares in this scenario were 64% for bortezomib, 25% for thalidomide and 11% for lenalidomide. The second scenario involved a steady increase of the uptake of lenalidomide to 50% of the market in year five. The third scenario evaluated a 20% increased uptake of the triple regimen carfilzomib, lenalidomide, and dexamethasone as a second-line of treatment. Direct drug costs were averaged from the listing prices across the five countries. The assumed annual treatment costs for the baseline scenario ranged between € 40 692 and € 40 781 per patient per year, while the total costs for an increased uptake of lenalidomide ranged between € 41 559 and € 44 139 per patient per year. The difference between both situations rose relatively steady from 2.13% of the total cost of the baseline scenario in year one to 8.23% of the baseline scenario in year five. Across all three scenarios the total treatment cost in the fifth year of treatment were lowest for the baseline scenario. For the increased uptake of lenalidomide in first-line therapy, the annual costs per patient in year five were € 44 139. For the 20% uptake of the triplet regimen as second-line treatment, the total increase in year five in total cost per patient and year was € 52 528 (45). A retrospective study based on United States claims data from 2006 to 2013 assessed patient monthly direct costs and cost patterns over quarterly time periods for patients with newly diagnosed MM treated with either bortezomib or lenalidomide based regimens. Costs were evaluated for 444 patients with newly diagnosed MM treated first-line with lenalidomide and 737 with bortezomib, for which data from treatment initiation until next treatment was available. For patients with first-line treatment with lenalidomide, the monthly treatment cost decreased steadily from US\$ 15 090 in the first to the third month since start of treatment to US\$ 5266 in month 19 or longer. In patients treated with firstline bortezomib the monthly costs fell from US\$ 16 126 in the first three months of treatment to US\$ 4833 in the 19th month or longer. Multivariable regression unadjusted for factors such as age, sex, number of prescriptions before index date for the beginning of first-line treatment, previous cancer history, etc. showed mean total cost of US\$ 7534 (standard deviation (SD) 3207) for patients treated first-line with lenalidomide, compared to US\$ 10 763 (SD 3938) in patients receiving first-line bortezomib. Monthly pharmacy costs included in the total monthly cost in the unadjusted analysis were US\$ 4101 (SD 1931) and US\$ 4855 (SD 2431) for lenalidomide and bortezomib, respectively (46).

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