Lenalidomide for 1st relapse multiple myeloma after bortezomib

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Summary

NICE recommends the use of lenalidomide for relapsed multiple myeloma only in those who have received two or more prior therapies.

The best available evidence to support the use of lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma comes from two phase III studies (MM-009 and MM-010). Both trials compared lenalidomide/dexamethasone to dexamethasone alone, and both trials used a primary endpoint of time to disease progression. There was only a limited number of patients in the two phase III studies who match the criteria for this application for funding, i.e., following one prior line of therapy - bortezomib. The time to progression was significantly longer for lenalidomide/dexamethasone compared to dexamethasone alone for both trials.

No studies have directly compared lenalidomide with other chemotherapy agents in the relapsed setting. It is also not clear whether/re-treatment with bortezomib after a suitable treatment-free interval would provide more benefit compared to using lenalidomide at first relapse following bortezomib, although the BCSH guideline states that re-exposure to the same treatment used at presentation is associated with increased rates of treatment resistance. Short remission duration with a given treatment is a strong indicator to employ an alternative regimen.

Stadtmauer EA et al, in their preplanned retrospective subgroup analysis of the two phase III studies, found that time to progression was significantly longer for patients who had received one prior therapy compared with those who had at least two prior therapies (17.1 months vs. 10.6 months; hazard ratio (HR) 0.68, 95% CI 0.48–0.97; P=0.026). PFS was also significantly longer in patients who had received two or more prior lines of therapy (median of 14.1 months vs. 9.5 months; HR 0.71, 95% CI 0.0–0.99; P=0.047). However, there were significant differences in baseline characteristics between the cohort who had received just one prior therapy and the cohort who had received two or more prior therapies, and one of those differences was the percentage who had received prior bortezomib therapy (1.5% vs. 11.4%; P<0.001).
Background

Multiple myeloma is a cancer of a type of white blood cell (plasma cell) in the bone marrow. In people with multiple myeloma, a single plasma cell becomes cancerous to form a myeloma cell, which begins to multiply. These abnormal plasma cells, or myeloma cells, build up in the bone marrow, reducing the space available for making normal white cells, red cells and platelets. Normal blood cells are responsible for fighting infections, carrying oxygen around the body and blood clotting. Myeloma cells produce large amounts of one type of abnormal antibody, which does not work properly and is not able to fight infection. Symptoms and clinical features of multiple myeloma include fatigue, bone pain and/or fracture, anaemia, infections, M-protein in serum and/or urine, and hypercalcaemia. The origin of multiple myeloma is unknown and malignant cells display a variety of cytogenetic abnormalities. Multiple myeloma is the second most common haematological cancer in the UK (1). In England and Wales there are approximately 4700 new diagnoses recorded annually. In 2009, most diagnoses were recorded in people aged 75–79 years. In the UK, the estimated lifetime risk of developing multiple myeloma is 1 in 115 for men and 1 in 155 for women (2).

Multiple myeloma remains an incurable disease, with an average survival of 4–6 years, but it can be treated with a combination of supportive measures and chemotherapy (1). The aim of treatment is to extend the length and quality of life by alleviating symptoms, controlling disease and minimising adverse effects. Survival after diagnosis can vary from months to more than 10 years. Factors affecting survival and outcome include burden of disease, type of cytogenetic abnormality, age and performance status, and response to treatment. In England and Wales the choice of first-line treatment (that is, treatment for treatment-naïve patients) depends on a combination of factors. Most people with multiple myeloma are not able to withstand intensive treatment, such as high-dose chemotherapy with stem cell transplantation, because of their age, other health problems or poor performance status. These people are offered single-agent or combination chemotherapy, which is less intensive. Typically, combination therapies include chemotherapy with an alkylating agent (such as melphalan or cyclophosphamide) and a corticosteroid (such as prednisolone or dexamethasone). More recent treatment options include drugs such as thalidomide and bortezomib. The main objective of first-line therapy is to achieve a period of stable disease (termed the plateau phase) for as long as possible, thereby prolonging survival and maximising quality of life. After initial treatment, most people usually experience a period of remission, but almost all relapse eventually, and some have disease that does not respond (is refractory) to treatment.

Lenalidomide

The National Comprehensive Cancer Network (NCCN) guideline on multiple myeloma recommends lenalidomide/dexamethasone as an option for salvage treatment of relapsed/refractory myeloma (3). The guideline also says that in patients who are steroid intolerant, lenalidomide monotherapy can be considered. An alternative option for patients relapsing after a period of time would be to re-treat the patient with the previous agent. However, the British Committee for standards in Haematology recommend in their 2010 guideline that re-exposure to the same treatment used at presentation is associated with increased rates of treatment resistance. Short remission duration with a given treatment is a strong indicator to employ an alternative regimen (13). For patients with progressive disease from first line therapy, the British Committee for standards in Haematology recommend a lenalidomide-containing regimen for multiple myeloma patients with ≥ grade 2 peripheral neuropathy (13). The 2009 International Myeloma Working Group guidelines recommend for primary salvage therapy the choice of combination therapy may depend on earlier exposure to a particular drug and concomitant co-morbidities, which might contra-indicate the delivery of a specific compound. Lenalidomide- or bortezomib-based regimens are also recommended for patients who relapse after thalidomide-based treatment. Patients with residual neuropathy following thalidomide- or bortezomib-based therapy may not tolerate either agent. For these patients, lenalidomide-based therapy is recommended (14).
NICE technology appraisal 171 recommends lenalidomide in combination with dexamethasone as an option for the treatment of multiple myeloma only in people who have received two prior therapies, with the following condition:

The drug cost of lenalidomide (excluding any related costs) for people who remain on treatment for more than 26 cycles (each of 28 days; normally a period of 2 years) will be met by the manufacturer (7).

Celgene do not operate a patient access scheme however the Revlimid® Options Scheme™ provides lenalidomide free-of-charge to all patients requiring treatment within the licensed indication for lenalidomide whether they fulfil the criteria for receiving it within National Institute for Health and Clinical Excellence (NICE) guidance or not (15).

Under the Revlimid® Options Scheme™, eligible patients will receive free-of-charge lenalidomide for all future treatment cycles beyond cycle 26, as long as they continue to satisfy the eligibility criteria. Physicians therefore have the freedom to continue prescribing lenalidomide for patients who are benefiting from treatment within licence, without incurring its cost.

Epidemiology
The annual incidence of relapsed and/or refractory multiple myeloma is approximately 3.9 per 100,000 population in the UK (8). At 1st relapse post bortezomib the estimated patient cohort is 1.13 per 100,000 population in the UK.

Published data
The best available evidence to support the use of lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma comes from two phase III studies (MM-009 and MM-010) (9, 10).

In both studies, adult patients were eligible if they had progressive multiple myeloma after at least one previous treatment, an ECOG performance status of 0–2, and had measurable disease that was not resistant to dexamethasone. Patients were assigned to receive oral lenalidomide 25mg or placebo on days 1–21 of a 28-day cycle. All patients also received 40mg of oral dexamethasone on days 1–4, 9–12, and 17–20. After the fourth cycle, 40mg of dexamethasone was administered only on days 1–4.

The primary endpoint for both studies was time to disease progression. Secondary endpoints included overall survival, response rate, and safety. The assignment of patients was stratified according to the level of serum β2-microglobulin, previous stem cell transplantation, and the number of previous anti-myeloma therapies. All primary analyses were based on the intention-to-treat population, and subgroup analyses were planned on the basis of stratification variables.

The results of each of the two phase III trials are summarised below:

**MM-009**
A total of 353 patients were enrolled, of which 177 were assigned to receive lenalidomide with dexamethasone (lenalidomide arm) and 176 to receive placebo with dexamethasone (placebo arm). The median age was 64 years in the lenalidomide arm and 62 years in the placebo arm (range 36–86 years). 91% of patients were ECOG performance status 0 or 1. 38% of patients had received one prior therapy, and 11% of patients had received bortezomib as a previous therapy (this will also include patients who had received 2 or more prior therapies).

After a median follow-up of 17.6 months, the median time to progression was significantly larger in all subgroups of patients who received lenalidomide compared with those who received placebo (P<0.001 for all comparisons), including patients who had received one previous therapy (median time not reached vs. 5.1 months). The median time to progression among the 39 patients who had received previous treatment with bortezomib was longer in the lenalidomide arm than in the placebo arm (10.3 months vs. 3.3 months, P<0.001). In the two study arms, prognostic factors for significant improvement in the time to progression included only one previous anti-myeloma therapy.

The median overall survival was significantly longer for patients in the lenalidomide arm than the placebo arm (29.6 months vs. 20.1 months; hazard ratio 0.44, 95% CI 0.3–0.65; P<0.001).

**MM-010**
A total of 351 patients were enrolled, of which 176 patients were assigned to lenalidomide and dexamethasone (lenalidomide arm) and 175 patients were assigned to placebo and dexamethasone (placebo arm). The median age was 63 years in the lenalidomide arm and 64 years in the placebo arm (range 33–84 years). 84% of patients had an ECOG performance status of 0 or 1. Patients in the two arms had received a median of two previous therapies (32% of patients had received 1 prior therapy) and 4.5% of patients had received bortezomib as a prior therapy (either as a first- or subsequent-line treatment).

At the time of the analysis, the median follow-up was 16.4 months. The median time to progression was 11.3 months in the lenalidomide arm and 4.7
months in the placebo arm (hazard ratio 2.85, 95% CI 2.16–3.76; P<0.001). The median time to progression for patients who had undergone one previous therapy was not reached in the lenalidomide arm and was 4.7 months in the placebo arm.

At the time of the last analysis, median overall survival had not been reached in the lenalidomide arm and was 20.6 months in the placebo arm (hazard ratio for death in the lenalidomide arm 0.66, 95% CI 0.45–0.96; P=0.03).

Additional analysis of phase III studies

Dimopoulos MA et al reported an updated pooled data analysis of 704 patients from the MM-009 and MM-010 phase III trials with an extended median follow-up of 48 months for overall survival (secondary endpoint) (11). Median overall survival was significantly longer in the lenalidomide arm than in the placebo arm (38 months vs. 31.6 months; P=0.045).

Stadtmauer EA et al performed a preplanned subset analysis of the two phase III studies evaluating the benefit of initiating lenalidomide and dexamethasone after only one prior therapy and compared outcomes for patients treated in later salvage therapy (12). The median age of patients who had received one prior therapy (133 patients) was 62.1 years and the median age for 2 or more therapies (220 patients) was 63.1 years. Significant baseline differences between patients receiving one prior therapy and two prior therapies included prior ASCT (66.9% vs. 53.2%; P=0.014); prior treatment with thalidomide (9.8% vs. 51.8%; P<0.001); and prior treatment with bortezomib (1.5% vs. 11.4%; P<0.001). The average length of time from diagnosis was also significantly different between patients with one prior therapy and those who had received two or more prior therapies (2.2 years vs. 4.1 years; P<0.001).

Patients with one prior therapy had a median treatment duration of 12.5 months (range 0.3–24.1) which was higher than that for patients with two or more prior therapies (9.2 months, range 0.03–24.8; P<0.001).

The proportion of patients who had a dose reduction and/or interruption of lenalidomide treatment were similar among those patients who had received one prior therapy and at least two prior therapies. The overall response rate was 66.9% for those receiving one prior therapy compared to 56.8% for those receiving two or more prior therapies; P=0.06. After a median follow-up of 15.5 months for responders, the median duration of response had not been reached for those receiving one prior therapy, and 13 months for those who had received two or more prior therapies (P=0.21). Time to progression was significantly longer for patients who had received one prior therapy compared with those who had at least two prior therapies (17.1 months vs. 10.6 months; hazard ratio (HR) 0.68, 95% CI 0.48–0.97; P=0.026). PFS was also significantly longer in patients who had received two or more prior lines of therapy (median of 14.1 months vs. 9.5 months; HR 0.71, 95% CI 0.2–0.99; P=0.047). Overall survival from study enrolment was significantly longer in patients who had received one prior therapy than in those who had received at least two prior therapies at the time of unblinding (median not reached vs. 30.8 months, HR 0.59, 95% CI 0.36–0.95; P=0.028). This survival advantage was also seen with extended follow-up (median overall survival 42 months vs. 35.8 months, P=0.041).

Safety

MM-009

Infections were more common in the lenalidomide arm than in the placebo arm (67.8% vs. 44%; P<0.001); grade 3 or 4 infections were noted in 38 patients (21.5%) and 21 patients (12%) respectively. Venous thromboembolic events were more common in the lenalidomide arm than in the placebo arm (14.7% vs. 3.4%, P<0.001).

Grade 3 or 4 haematological events occurred in 52.5% of patients in the lenalidomide arm and 13.7% of patients in the placebo arm (P<0.001). Grade 3 or 4 neutropenia was more common in the lenalidomide arm than in the placebo arm (41.2% vs. 4.6%, P<0.001), as was thrombocytopenia (14.7% vs. 6.9%, P=0.02).

Thirty-five patients (19.8%) in the lenalidomide arm and 18 patients (10.2%) in the placebo arm discontinued the study drug because of adverse events.

MM-010

Patients in the lenalidomide arm had a higher incidence of grade 3 neutropenia (25%) than patients in the placebo arm (2.3%). Grade 3 or 4 thrombocytopenia was twice as frequent in the lenalidomide arm as in the placebo arm (11.4% vs. 5.7%). Lenalidomide was associated with higher incidence of deep-vein thrombosis (4% vs. 3.5%) and pulmonary embolism (4.5% vs. 1.2%) than placebo.

Dose reduction or interruption because of adverse events was more common in the lenalidomide arm than in the placebo arm (76.1% vs. 56.9%, P<0.001). There were 11 deaths that were possibly related to a study drug (5 in the lenalidomide arm and 6 in the placebo arm). 31 patients in the two arms (8.8%) discontinued treatment early because of adverse events.
There has been recent healthcare professional communication regarding an increased risk of hepatic disorders. The following information has been issued as a consequence:

In multiple myeloma patients treated with lenalidomide in combination with dexamethasone, some severe cases of liver injuries, including fatal cases, have been reported: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis and mixed cytolytic/cholestatic hepatitis.

Lenalidomide is excreted by the kidneys. It is important to adjust the dose of lenalidomide in patients with renal impairment to avoid high plasma levels which may increase the risk of more severe haematological side effects or hepatotoxicity.

The mechanisms of severe drug-induced hepatotoxicity remain unknown and risk factors might be pre-existing viral liver disease, elevated baseline liver enzymes, and possibly treatment with antibiotics.

Monitoring of liver function is recommended, particularly when there is a history of, or concurrent, viral liver infection or when lenalidomide is combined with medications known to be associated with liver dysfunction such as paracetamol.

**Cost**

Eleven months treatment in the phase III trials equates to approximately 12 cycles of treatment (28 days per cycle). The drug acquisition cost of one cycle for 25mg lenalidomide daily is £5240 per patient (including VAT). The acquisition cost for the 12 cycles would be £62,900 per patient (including VAT).

Assuming epidemiology of 1.13/100,000, the drug acquisition cost per 100,000 population would be £5,920 per cycle and £71,050 for the 12 cycles (both including VAT).

The regimen also includes concomitant dexamethasone but the cost of dexamethasone has not been included here.

**Service implication**

Lenalidomide is an oral medication, and its normal comparator would be bortezomib, which is an intravenous medication. However, as per this application to the CDF, bortezomib would be administered first line before lenalidomide. Therefore, the capacity of the outpatient cancer day units would not be expected to significantly change.

**Summary**

NICE recommends the use of lenalidomide for relapsed multiple myeloma only in those who have received two or more prior therapies.

The best available evidence to support the use of lenalidomide and dexamethasone for the treatment of relapsed or refractory multiple myeloma comes from two phase III studies (MM-009 and MM-010). Both trials compared lenalidomide/dexamethasone to dexamethasone alone, and both trials used a primary endpoint of time to disease progression. There was only a limited number of patients in the two phase III studies who match the criteria for this application for funding, i.e. following one prior line of therapy- bortezomib. The time to progression was significantly longer for lenalidomide/dexamethasone compared to dexamethasone alone for both trials.

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per month/ cycle</th>
<th>Cost per 100,000 population per month/ cycle</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>Multiple myeloma that has relapsed after bortezomib first-line therapy</td>
<td>1.13</td>
<td>Around 11 months for time to progression which equates to 12 cycles approximately</td>
<td>£5240 per cycle</td>
<td>£5920 per cycle</td>
<td>£71,050</td>
</tr>
</tbody>
</table>

**Reference**

15. The Revlimid® Options Scheme™. Date accessed January 2013 [http://www.celgene.co.uk/hcp_revlimid_options_scheme.aspx](http://www.celgene.co.uk/hcp_revlimid_options_scheme.aspx)
Details of search strategy:

In house database
NeLM

1. EMBASE; LENALIDOMIDE/; 5969 results.
2. EMBASE; MULTIPLE MYELOMA/; 41280 results.
3. EMBASE; 1 AND 2; 3145 results.
4. EMBASE; "LENALIDOMIDE/"; 1528 results.
5. EMBASE; 2 AND 4; 840 results.
6. EMBASE; "MULTIPLE MYELOMA/"; 26216 results.
7. EMBASE; 4 AND 6; 636 results.
8. EMBASE; 7 [Limit to: Human and English Language and (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial)]; 181 results.
9. MEDLINE; lenalidomide.ti,ab; 1482 results.
10. MEDLINE; MULTIPLE MYELOMA/; 29473 results.
11. MEDLINE; 9 AND 10; 676 results.
12. MEDLINE; "MULTIPLE MYELOMA/"; 22686 results.
13. MEDLINE; 9 AND 12; 642 results.
14. MEDLINE; 13 [Limit to: English Language and Humans and Publication Year 2010-Current]; 362 results.
15. EMBASE; 8 [Limit to: Human and English Language and (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial) and Publication Year 2010-Current]; 93 results.
16. MEDLINE; 13 [Limit to: English Language and Humans and Publication Year 2000-2009]; 254 results.
17. MEDLINE; 13 [Limit to: English Language and Humans]; 616 results.
18. EMBASE; 8 [Limit to: Human and English Language and (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial) and Publication Year 2000-2009]; 88 results.
19. MEDLINE, EMBASE; Duplicate filtered: [13 [Limit to: English Language and Humans and Publication Year 2010-Current]], [8 [Limit to: Human and English Language and (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial) and Publication Year 2010-Current]]; 455 results.
20. MEDLINE, EMBASE; Duplicate filtered: [13 [Limit to: English Language and Humans and Publication Year 2000-2009]], [8 [Limit to: Human and English Language and (Clinical Trials Clinical Trial or Randomized Controlled Trial or Controlled Clinical Trial or Phase 2 Clinical Trial or Phase 3 Clinical Trial or Phase 4 Clinical Trial) and Publication Year 2000-2009]]; 342 results.

The document reflects the views of LCNDG and may not reflect those of the reviewers

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