Lenalidomide becomes standard of care for multiple myeloma in the maintenance setting

The treatment of multiple myeloma has been revolutionized in the past few decades, with the introduction of numerous novel drug classes that have more than doubled median survival times. The immunomodulatory drug (IMiD), lenalidomide, forms the backbone of the majority of treatment paradigms, first receiving US Food and Drug Administration approval in 2006 for use in combination with dexamethasone in previously treated patients with multiple myeloma. Since then, approved indications for lenalidomide in multiple myeloma have continued to expand.

Most recently, on February 22, 2017, lenalidomide was approved for use as maintenance therapy following autologous stem cell transplant (ASCT), making it the first and only treatment available in this setting. This approval was based on 2 randomized, controlled trials that evaluated the efficacy and safety of lenalidomide in more than 1,000 patients in this setting and demonstrated a significant advantage in progression-free survival (PFS) compared with patients receiving placebo.

CALGB 100104[1] and IFM 2005-02[2] were randomized, double-blind phase 3 trials conducted at 47 locations across the United States and 78 centers in France, Belgium, and Switzerland, respectively. In the CALGB trial, eligible patients were 18-70 years of age, with a European Cooperative Oncology Group (ECOG) performance status of 0 or 1, symptomatic disease requiring treatment (Durie-Salmon stage ≥1), and who received any induction therapy of 2-12 months duration. In the IFM trial, eligible patients were younger than 65 years, with multiple myeloma that had not progressed in the interval between first-line ASCT, performed within the previous 6 months, and randomization, and who had normal liver function tests and blood cell counts.

In CALGB 100104, after undergoing ASCT, 460 patients were randomly assigned to lenalidomide (starting at a dose of 10 mg/day) or placebo between day 100 and day 110 after transplantation. In IFM 2005-02, after undergoing ASCT, 614 patients were randomized 1:1 to receive either consolidation treatment with lenalidomide (at a dose of 25 mg/day on days 1-21 of each 28-day cycle for 2 cycles) followed by maintenance with lenalidomide (10 mg/day for the first 3 months, increasing to 15 mg if tolerated), or the same consolidation treatment followed by maintenance therapy with placebo.

The primary endpoint of CALGB 100104 was time to progression (TTP) and lenalidomide was associated with a significantly longer TTP. Median PFS was also improved by around 15 months (hazard ratio [HR], 0.38; $P < .001$). In a more recent long-term PFS analysis, median PFS was 5.7 years in the lenalidomide arm compared with 1.9 years with placebo, a difference of 3.8 years (HR, 0.38).[3]

The primary endpoint for IFM 2005-02 was PFS and lenalidomide maintenance therapy resulted in a significant

What's new, what's important

Lenalidomide's most recent approval as maintenance therapy after ASCT in patients with multiple myeloma, made it the first and only treatment available in this setting. The approval was based on findings from 2 randomized, controlled trials that evaluated the efficacy and safety of lenalidomide in this setting and demonstrated a significant advantage in PFS compared with placebo. In the CALGB 100104 trial, lenalidomide maintenance therapy was associated with a significantly longer TTP and median PFS, improved by 15 months (long-term PFS analysis, 5.7 years vs 1.9 years with placebo). In the IFM 2005-02, lenalidomide resulted in a significant improvement in PFS (most recent: 3.9 vs 2 years, respectively). Pooled data from a meta-analysis of the 2 studies (GIMEMA-RVMM-PI-209) showed that lenalidomide after frontline treatment with high-dose melphalan and ASCT reduced the risk of death by 26% compared with placebo or no maintenance therapy. The most common AEs across both studies included neutropenia, thrombocytopenia, and leukopenia among others. AEs were generally most common in the first 6 months of treatment then declined in frequency or remained stable. The prescribing information includes warnings and precautions about embryo-fetal toxicity, hematologic toxicity, venous/arterial thromboembolic events, secondary primary malignancies, hepatotoxicity, and allergic reactions. Given its teratogenic effects, lenalidomide is only available through a restricted program under a risk evaluation mitigation strategy.

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Mechanism of action: lenalidomide

Unique MoA ties together many cellular effects. Lenalidomide is a derivative of thalidomide, a drug renowned for its disastrous effects on developing fetuses when it was used as a cure for morning sickness in the 1950s. These drugs also have powerful anticancer effects, originally thought to derive from their anti-inflammatory properties, hence their moniker 'immunomodulatory drugs' (IMiDs).

Lenlidomide and other IMiDs have revolutionized the treatment of patients with multiple myeloma, with lenalidomide securing its first regulatory approval in the United States in 2006 for this indication. Over the years, a number of other potential anticancer mechanisms for lenalidomide have been proposed, including anti-angiogenic properties, modulation of the tumor microenvironment and direct effects on the cancer cells.

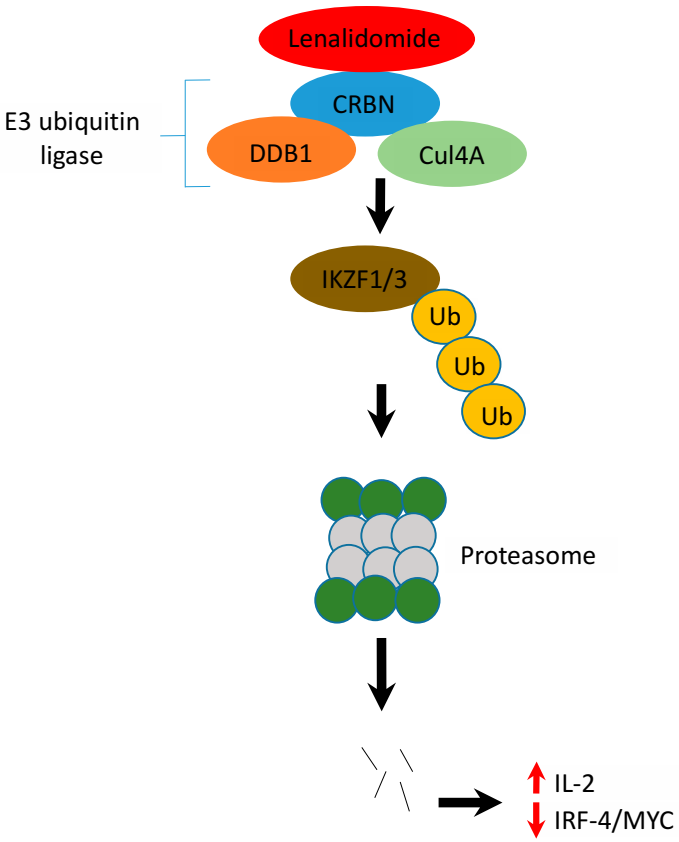
More recently, a common mechanism of action that ties many of the cellular effects of lenalidomide and other IMiDs together has been uncovered. Lenalidomide has been found to bind to a protein called cereblon, which forms part of an ubiquitin ligase complex in the cell.

Ubiquitin ligases are responsible for tagging proteins with ubiquitin molecules that are recognized by the cell's waste disposal machinery, the proteasome, which removes these unwanted or damaged proteins from the cell by breaking them down into pieces.

Cereblon is responsible for substrate recognition, in other words it finds the target proteins that will be tagged with ubiquitin and marked for destruction. The binding of lenalidomide to cereblon changes its substrate specificity, meaning that it recruits different target proteins. Most relevant to the anticancer activity of lenalidomide are 2 particular targets, the ikaros family zinc finger (IKZF) transcription factors, IKZF1 and IKZF3.

These transcription factors regulate the expression of a number of different genes, including interferon regulatory factor 4 (*IRF4*), which in turn triggers expression of *MYC*, whose protein product is known to play an important role in cell proliferation and growth, and the interleukin-2 (*IL-2*) gene, that is involved in the immune response, though in this case IKZF1/3 actually represses expression of the gene.

In the presence of lenalidomide, IKZF1 and IKZF3 are targeted for destruction by the proteasome, their downstream effects on *MYC* and *IL-2* are lost, resulting in reduced expression of *MYC* and increased expression of *IL-2*. This helps to explain some of the observed anticancer effects of lenalidomide, including its direct effects on cancer cells, mediated through *MYC*, and its immunomodulatory properties, mediated through *IL-2*. This is a unique mechanism of action and offers a way of targeting transcription factors, which until now have generally been regarded as undruggable.



Lenalidomide exerts a range of different anti-tumor effects primarily through its binding to the cereblon protein, the substrate recognition component of an ubiquitin ligase complex that tags unwanted or damaged proteins for destruction by the proteasome. Binding of lenalidomide changes the specificity of cereblon, causing it to target, among other proteins, 2 transcription factors, IKZF1 and IKZF3. The downstream effects of these transcription factors are lost, resulting in reduced expression of MYC, which reduces cancer cell growth and proliferation, and increased expression of IL-2, which promotes the anti-tumor immune response. Figure created by Jane de Lartigue, PhD

IL-2, interleukin-2; IRF-4, interleukin regulatory factor 4; Ub, ubiquitin; CRBN, cereblon; DDB1, DNA damage binding protein 1; Cul4A, cullin 4A; IKZF1/3, ikaros family zinc finger 1/3.

improvement in PFS in both the originally published study (18-month PFS advantage) and long-term follow-up. The most recent PFS analysis demonstrated a PFS of 3.9 years for lenalidomide, compared with 2 years for no maintenance, a difference of 1.9 years (HR, 0.53). Although the studies were not powered for an overall survival (OS) endpoint, a descriptive analysis showed a median OS of 9.3 years, compared with 7 years in CALGB 100104, and 8.8

years compared with 7.3 years in IFM 2005-02.

In a meta-analysis of data pooled from these 2 studies and a third randomized trial (GIMEMA-RVMM-PI-209),[4] which was presented at the 2016 annual meeting of the American Society of Clinical Oncology, maintenance therapy with lenalidomide following frontline treatment with high-dose melphalan and ASCT reduced the risk of death by 26% compared with placebo or no maintenance therapy, prompting suggestions that lenalidomide become standard of care in this setting.

The safety profile of lenalidomide in this setting was similar to that previously described in other studies. The most frequently reported adverse events (AEs), across both studies, were neutropenia, thrombocytopenia, leukopenia, anemia, upper respiratory tract infection, bronchitis, nasopharyngitis, cough, gastroenteritis, diarrhea, rash, fatigue, asthenia, muscle spasm, and pyrexia. The most common grade 3/4 AEs included neutropenia, thrombocytopenia, and leukopenia. AEs were generally most common in the first 6 months of treatment and subsequently declined in frequency over time or remained stable.

The prescribing information carries warnings and precautions about embryo-fetal toxicity, hematologic toxicity, venous/arterial thromboembolic events, secondary primary malignancies, hepatotoxicity, allergic reactions, tumor lysis syndrome, and thyroid disorders.[5] Given its teratogenic effects, lenalidomide is only available through a restricted program under a risk evaluation mitigation strategy.

Patients with neutropenia should be monitored for signs of infections, patients advised to look for signs of bleeding or bruising, and weekly complete blood count performed for the first 2 cycles, on days 1 and 15 of cycle 3 and every 4 weeks thereafter.

Action should be taken to try to reduce the risk of venous and arterial thromboembolic events where possible and thrombophylaxis is recommended, based on the assessment of the underlying risk. Since lenalidomide can increase the risk of secondary primary malignancies, each case should be evaluated for risk-to-benefit ratio.

Liver enzymes should be monitored periodically and treatment interrupted upon their elevation, resuming at a lower dose if levels return to baseline values. Patients who have a history of grade 4 rash following thalidomide treatment should not receive lenalidomide. If grade 2-3 skin rash occurs, treatment interruption or discontinuation should be considered and lenalidomide should be discontinued in the event of angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome or toxic epidermal necrolysis are suspected.

Patients with high tumor burden prior to treatment are at highest risk of tumor lysis syndrome and should be monitored closely and appropriate precautions taken, and thyroid function should be measured before and during lenalidomide treatment to address potential thyroid disorders. Lenalidomide is marketed as Revlimid by Celgene Corporation.

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